Protocol Number: ADCT-301-103

Official Title: A Phase 1b, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of Camidanlumab Tesirine (ADCT-301) as Monotherapy or in Combination in Patients With Selected Advanced Solid Tumors

NCT Number: NCT03621982

Document Date: 14 February 2022

CLINICAL STUDY PROTOCOL

IND: 139357
EudraCT Number: 2019-003132-23

A Phase 1b, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of Camidanlumab Tesirine (ADCT-301) as Monotherapy or in Combination in Patients With Selected Advanced Solid Tumors

PROTOCOL NO.: ADCT-301-103

Sponsor: **ADC Therapeutics SA**
[redacted]

Sponsor Contact: [redacted]
Medical Director Clinical Development
ADC Therapeutics UK
email: [redacted]

Date of Amendment 8 14 February 2022

Confidentiality Statement

[redacted]

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title	A Phase 1b, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of Camidanlumab Tesirine (ADCT-301) as Monotherapy or in Combination in Patients With Selected Advanced Solid Tumors
Protocol Number	ADCT-301-103
Date of Amendment 8	14 February 2022

Protocol accepted and approved by:

[redacted]
Medical Director Clinical Development
ADC Therapeutics UK
email: [redacted]

Signature: [redacted]
Email:

Signature Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled: "A Phase 1b, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of Camidanlumab Tesirine (ADCT-301) as Monotherapy or in Combination in Patients With Selected Advanced Solid Tumors" and the accompanying Investigator's Brochure (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 8, dated 14 February 2022, the current version of International Council for Harmonisation (ICH) harmonised tripartite guideline E6: Good Clinical Practice, and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics SA or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer the study drug only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ADC Therapeutics SA.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Printed Name of Institution

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
AESI	adverse event of special interest
AI	accumulation index
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration-time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration-time curve from time zero to the end of the dosing interval
BOR	best overall response
BP	blood pressure
BID	twice daily
β-HCG	human chorionic gonadotropin
[redacted]	[redacted]
[redacted]	[redacted]
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
cHL	classical Hodgkin Lymphoma
CHPi	checkpoint inhibitor
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CMV	cytomegalovirus

Abbreviation	Definition
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated protein 4
COVID-19	Coronavirus disease 19
DESC	dose-escalation steering committee
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
ECG	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FIH	first-in-human
GBS	Guillain-Barré syndrome
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
[redacted]	[redacted]
GGT	gamma glutamyl transferase
GI	gastrointestinal

Abbreviation	Definition
h	hour
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HSV1	herpes simplex virus 1
HSV2	herpes simplex virus 2
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune-confirmed progressive disease
iCR	immune-complete response
IEC	independent ethics committee
IL	interleukin
imRECIST	immune-modified Response Evaluation Criteria in Solid Tumors
INR	international normalized ratio
iPR	immune-partial response
IRB	institutional review board
iRECIST	immune-RECIST (modified RECIST 1.1 for immune-based therapeutics)
irRC	immune-related Response Criteria
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
iSD	immune-stable disease
iUPD	immune-unconfirmed progressive disease
IV	intravenous
IVIg	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
min	minute
mmHg	millimeters of mercury
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability

Abbreviation	Definition
MSS	microsatellite stability
MTD	maximum tolerated dose
NHL	non-Hodgkin lymphoma
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBD	pyrrolobenzodiazepine
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PLEX	plasma exchange
PR	partial response
PTT	partial thromboplastin time
QT	measure between Q wave and T wave in the electrocardiogram
QTcB	Bazett correction of the QT measure
QTcF	Fridericia correction of the QT measure
Q3W	every 3 weeks
RBC	red blood cell
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SoC	standard of care
SoE	Schedule of Events
sCD25	soluble CD25
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics

Abbreviation	Definition
[redacted]	[redacted]
TEAE	treatment-emergent adverse event(s)
Teff	effector T cell
TEN	Topic epidermal necrolysis
TGF-β	Tumor growth factor beta
T_{half}	apparent terminal elimination half-life
[redacted]	[redacted]
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TNBC	triple negative breast cancer
Treg	regulatory T cell
TSH	thyroid stimulating factor
ULN	upper limit of normal
US	United States
V_d	volume of distribution
VZV	varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

SUMMARY OF CHANGES

The primary reason for Protocol Amendment 8 is to extend the contraception period after last dose of camidanlumab tesirine, following an urgent safety measure. The contraception period is determined based on the compound properties and half-life, and has been updated due to recently revised half-life value of camidanlumab tesirine.

- In Section 5.1, Inclusion criterion 11: For women of childbearing potential, the period of contraception after last dose of camidanlumab tesirine has been extended to at least 9.5 months. For men with female partners who are childbearing potential, the period of abstinence or use of condom has been extended to at least 6.5 months after last dose of camidanlumab tesirine. Section 7.4.6 Pregnancy Test, Section 8.6 Pregnancy Reporting and Schedule of Assessments (Table 2) have been revised accordingly.
- In addition, revisions to the protocol text have also been applied to the synopsis section.

LIST OF PRIOR PROTOCOL VERSIONS

Versions	Version Date	Rationale for Changes
Protocol Amendment 7	02 September 2021	The primary reason for Protocol Amendment 7 is to further specify the patient population to be enrolled in the Dose-Expansion Group 2. Group 2 will be a basket group enrolling patients with advanced/metastatic solid tumors and MSI-H/dMMR status, who received a prior regimen containing a PD-1/PD-L1 inhibitor, for which the best response was CR, PR, or SD ≥4 months, and then progressed while continuing on the PD-1/PD-L1 inhibitor-based regimen
Protocol Amendment 6	12 January 2021	The primary reason for Protocol Amendment 6 is to include additional safety measures (such as management of potential autoimmune adverse events), extend the duration of contraception for women of childbearing potential, implement mandatory influenza, and severe acute respiratory syndrome coronavirus (SARS-CoV2) testing, within 3 to 5 days or less prior to initiation of the study drug. The recommendation of varicella zoster virus (VZV) prophylaxis is added as per applicable guidelines. The sample schedule has been corrected. In addition, inclusion criteria have been updated to include patients with life expectancy ≥3 months and specified the need for mutational status for selected solid tumor types.
Protocol Amendment 5	13 July 2020	The primary reason for Protocol Amendment 5 is to add the investigation of dose-escalation and dose-expansion, for a combination of camidanlumab tesirine and a checkpoint inhibitor (CHPi), pembrolizumab.
Protocol Amendment 4	15 February 2020	The primary reason for Protocol Amendment 4 is to add a section for inclusion of patients recently treated with checkpoint inhibitors (3 to 6 weeks prior to camidanlumab tesirine). In addition, relevant updates in line with study needs have been introduced.
Protocol Amendment 3	15 July 2019	The primary reasons for Protocol Amendment 3 were to add a section for adverse events of special interest (AESIs) and set the washout period of systemic anticancer immunotherapies to 4 weeks prior to start of study drug.
Protocol Amendment 2	05 March 2019	The primary reasons for Protocol Amendment 2 (05 March 2019) were to include another solid tumor indication (colorectal cancer) and to possibly add the enrollment of approximately 12 patients in paired-biopsy cohorts in which patients will have a mandatory on-treatment biopsy [redacted].

Versions	Version Date	Rationale for Changes
Protocol Amendment 1	20 June 2018	The basis for Protocol Amendment 1 (20 June 2018) is the request from the Food and Drug Administration (FDA) to modify the study stopping rules to be consistent with the recent comments from the FDA related to the studies ADCT-301-001 and ADCT-301-002.
Original Protocol	11 May 2018	

PROTOCOL SYNOPSIS

Protocol Number:	ADCT-301-103
Title:	A Phase 1b, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of Camidanlumab Tesirine (ADCT-301) as Monotherapy or in Combination in Patients With Selected Advanced Solid Tumors
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 1b
Indication:	Selected advanced solid tumors
Rationale:	One of the factors with particular impact on the effect of tumor eradication through the immune system is the intra-tumoral balance of effector T cells (Teffs) versus regulatory T cells (Tregs). Therefore, attempts are currently made to either increase the amount of CD8(+) Teffs or decrease the amount of CD25(+) Tregs. Such depletion or inhibition of CD25(+) Tregs may offer stand alone or additional therapeutic benefit in combination with a checkpoint inhibitor. Camidanlumab tesirine, an antibody-drug conjugated (ADC) targeting human CD25, is a candidate for selectively depleting CD25(+) Tregs in tumor infiltrates. Moreover, the intra-tumor release of its pyrrolobenzodiazepine (PBD) warhead may cause bystander killing of neighboring tumor cells. In addition, the PBD warhead will trigger immunogenic cell death, which in turn will strengthen the immune response against tumor cells.
Objectives:	**Primary Objective** • Characterize the safety and tolerability of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab, and to identify the recommended dose(s) and schedule(s) for future studies in patients with selected advanced solid tumors **Secondary Objectives** • Evaluate the preliminary anti-tumor activity of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab • Evaluate the pharmacokinetic (PK) profile of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab • Evaluate the immunogenicity of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab [redacted]

Endpoints:

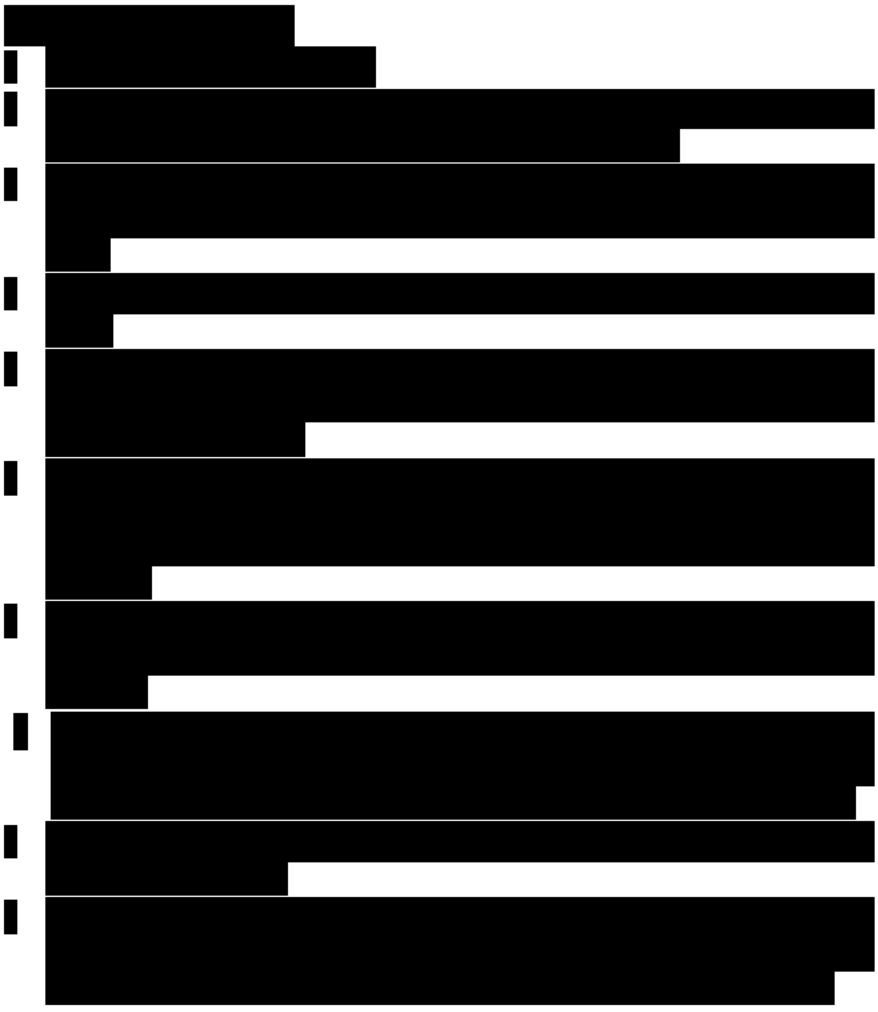
Primary Endpoints

- Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab
- Changes from Baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs) for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab
- Frequency of dose interruptions and dose reductions for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab
- Incidence of dose limiting toxicities (DLTs) (dose-escalation only) for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab

Secondary Endpoints

- Overall response rate (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab
- Duration of response (DOR) defined as the time from the first documentation of tumor response to disease progression, as per RECIST v1.1, or death for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab
- Progression-free survival (PFS) defined as the time between start of treatment and the first documentation of recurrence, progression, as per RECIST v1.1, or death for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab

- Overall survival (OS) defined as the time between the start of treatment and death from any cause for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab
- Concentrations and PK parameters of camidanlumab tesirine total antibody, PBD-conjugated antibody, and unconjugated warhead SG3199 in serum
- Frequency of confirmed positive anti-drug antibody (ADA) responses, their associated titers and, if applicable, neutralizing activity to camidanlumab tesirine after treatment with camidanlumab tesirine



Study Design:

This is a Phase 1b, multi-center, open-label study with a dose-escalation part and a dose-expansion part.

In the dose-escalation part (Part 1), patients will receive escalating doses of camidanlumab tesirine as monotherapy, or escalating dose of camidanlumab tesirine in combination with pembrolizumab, guided by a 3+3 design.

Additionally, in the dose-escalation part for camidanlumab tesirine as monotherapy, separate paired-biopsy cohorts have been included:

- The paired-biopsy cohorts will enroll patients, treated only with camidanlumab tesirine as monotherapy, who will be undergoing two mandatory biopsies, one pre- and one on-treatment biopsy, [redacted] These cohorts will be introduced at dose levels that have been deemed safe during escalation. In order to allow patients to benefit from trial participation, one intra-patient dose-escalation (after the mandatory on-treatment biopsy has been obtained) to the highest dose level determined to be safe at that point will be performed, unless deemed by the Investigator not to be in the best interest of the patient.

Two groups are planned in the dose-expansion part (Part 2):

- Group 1: an indication for which camidanlumab tesirine in combination with pembrolizumab at the doses shown in Part 1 to have preliminary activity.
- Group 2: a basket group of patients with advanced solid tumors and MSI-H/dMMR status, who have received a prior regimen containing a PD-1/PD-L1 inhibitors, for which the best response was CR, PR, or SD ≥4 months, and then progressed while under treatment with the PD-1/PD-L1 inhibitor based regimen; no more than 4 patients with the same indication are allowed in this basket group.

Patient Selection:

Inclusion Criteria:

1. Written informed consent must be obtained prior to any procedures.
2. Male or female patient aged 18 years or older.
3. Pathologic diagnosis of solid tumor malignancy that is locally advanced or metastatic at time of Screening:
   - Part 1 Dose-escalation camidanlumab tesirine as monotherapy:

     Selected advanced solid tumors: colorectal, head and neck squamous cell carcinoma, non-small cell lung cancer, gastric and esophageal cancers, pancreas, bladder, renal cell carcinoma, melanoma, triple negative breast cancer, and ovarian/fallopian tube cancer.
   - Part 1 Dose-escalation camidanlumab tesirine in combination with pembrolizumab:

     Selected advanced solid tumors: colorectal cancer, gastric-esophageal cancer, ovarian/fallopian tube cancer, pancreatic cancer, non-small cell lung cancer, and melanoma.

     Note: For colorectal cancer, gastric-esophageal cancer, ovarian/fallopian tube cancer, pancreatic cancers MMR/MSS/MSI status is mandatory. If MMR/MSS/MSI status is not available at signature of the informed consent, the test should be performed before C1D1.

- Part 2 Dose-expansion camidanlumab tesirine in combination with pembrolizumab:
  - Group 1: One of the indications identified in Part 1, for which at least 1 response (PR or CR) was seen.
  - Group 2: Patients with advanced solid tumors and MSI-H/dMMR status, who have received a prior regimen containing PD-1/PD-L1 inhibitors, for which the best response was CR, PR, or SD ≥4 months, and then progressed while under treatment with the PD-1/PD-L1 inhibitor-based regimen

    Note: A maximum of 4 patients with the same indication will be allowed in this basket group.

4. Patients who are refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.
5. Patients with advanced/metastatic cancer, with measurable disease as determined by RECIST v1.1 or immune-related Response Criteria (irRC)/ immune-related Response Evaluation Criteria In Solid Tumors (irRECIST)/ immune-related Response Evaluation Criteria In Solid Tumors (iRECIST)/ immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST) as per Investigator discretion.

   Note 1: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) can be considered as measurable lesions ONLY if the soft tissue component meets the definition of measurability per RECIST.

   Note 2: If immediate prior therapy contains an immune-therapy component, progression has to meet criteria as defined in irRC/irRECIST/iRECIST/imRECIST as per Investigator discretion.
6. A) For camidanlumab tesirine as monotherapy: Patient must have a site of disease amenable to biopsy and be willing to undergo fresh biopsy procedures (minimum 3 passes each) prior to first dose, according to the treating institution's guidelines.

   B) Patients included in the paired-biopsy cohort must in addition be willing to undergo fresh biopsy procedures (minimum 3 passes each) after receiving at least one dose of study drug.

   C) For camidanlumab tesirine in combination with pembrolizumab:

   Patient must either have a site of disease amenable to biopsy and must provide fresh tumor biopsy prior to C1D1, or have sufficient available archival tumor tissue (biopsied after their last disease progression, and in the situation where the patient has received no additional anti-cancer therapy between their progression and C1D1). Patients must also be willing to undergo fresh biopsy procedures (minimum 3 passes each) after receiving at least 1 dose of study treatment, according to the treating institution's guidelines.
7. ECOG performance status 0-1.
8. Patient with life expectancy ≥3 months as per Investigator assessment.

9. Adequate organ function as defined by screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) ≥1.5 × 10^3/μL (off growth factors at least 72 hours).
   b. Platelet count ≥100 × 10^3/μL without transfusion in the past 10 days.
   c. Hemoglobin ≥9 g/dL (5.6 mmol/L) (prior transfusion allowed).
   d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma glutamyl transferase (GGT) ≤2.5 × the upper limit of normal (ULN) if there is no liver involvement; ALT or AST ≤5 × ULN if there is liver involvement.
   e. Total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 × ULN with direct bilirubin ≤1.5 × ULN).
   f. Blood creatinine ≤1.5 × ULN or calculated creatinine clearance ≥60 mL/min by the Cockcroft-Gault equation.

   Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.
10. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to start of study drug for women of childbearing potential (WOCBP).
11. Women of childbearing potential must agree to use a highly effective method of contraception from the time of giving informed consent until at least 9.5 months after the last dose of camidanlumab tesirine or 4 months after last dose of pembrolizumab, whichever is the latest. Men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of giving informed consent until at least 6.5 months after the patient receives his last dose of camidanlumab tesirine or 4 months after last dose of pembrolizumab, whichever is the latest.

Exclusion Criteria:

1. Participation in another investigational interventional study.
2. Prior therapy with a CD25 (IL-2R) antibody.
3. Known history of ≥Grade 3 hypersensitivity to a therapeutic antibody.
4. Patients with prior solid organ or allogeneic bone marrow transplant.
5. History of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]) (patients with vitiligo, type 1 diabetes mellitus, residual hypothyroidism, hypophysitis due to autoimmune condition only requiring hormone replacement may be enrolled).
6. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome and myasthenia gravis) or other central nervous system (CNS) autoimmune disease (e.g., poliomyelitis, multiple sclerosis).

7. History of recent infection (within 4 weeks of C1D1) caused by a pathogen known to be associated with GBS, for example: herpes simplex virus 1/2 (HSV1, HSV2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

   Note: An influenza test and a pathogen-directed SARS-CoV-2 test (such as polymerase chain reaction [PCR]) are mandatory and must be negative before initiating study treatment (tests to be performed 3 days or less prior to dosing on C1D1; an additional 2 days are allowed in the event of logistical issues for receiving the results on time).
8. Known seropositive and requiring anti-viral therapy for human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV). Note: Testing is not mandatory to be eligible but should be considered in patients with high risk for these infections; testing is mandatory if status is unknown.
9. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.
10. Failure to recover to ≤Grade 1 (Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]) from acute non-hematologic toxicity (to ≤Grade 2 for neuropathy or alopecia), due to previous therapy, prior to screening.
11. Symptomatic CNS metastases or evidence of leptomeningeal disease (brain MRI or previously documented cerebrospinal fluid [CSF] cytology). Previously treated asymptomatic CNS metastases are permitted provided that the last treatment (systemic anticancer therapy and/or local radiotherapy) was completed ≥4 weeks prior to Day 1 except usage of low dose of steroids on a taper (i.e., up to 10 mg prednisone or equivalent on Day 1 and consecutive days is permissible if being tapered down). Patients with discrete dural metastases are eligible.
12. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath).
13. Active diarrhea CTCAE Grade 2 or a medical condition associated with chronic diarrhea (such as irritable bowel syndrome, inflammatory bowel disease).
14. Active infection requiring systemic antibiotic therapy.
15. Active bleeding diathesis or significant anticoagulation (international normalized ratio [INR] ≥2.0).
16. Breastfeeding or pregnant.

17. Significant medical comorbidities, including uncontrolled hypertension (blood pressure [BP] ≥160 mmHg systolic and/or ≥110 mmHg diastolic repeatedly with or without anti-hypertensive medication), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, severe uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, active ulceration of the upper gastrointestinal (GI) tract or GI bleeding, or severe chronic pulmonary disease.
18. Major surgery, radiotherapy, chemotherapy or other anti-neoplastic therapy within 14 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor. For cytotoxic agents that have major delayed toxicity, e.g., mitomycin C and nitrosoureas, 4 weeks is indicated as washout period. For patients receiving systemic anticancer immunotherapies (as opposed to intralesional) that lead to activation of Teffs and/or increase the Teff/Treg ratio, such as anti-PD-1 antibodies, 4 weeks are indicated as the washout period.
19. Use of any other experimental medication within 14 days prior to start of study drug (C1D1).
20. Patients requiring concomitant immunosuppressive agents or chronic treatment with corticosteroids except:
    - replacement dose steroids in the setting of adrenal insufficiency
    - topical, inhaled, nasal, and ophthalmic steroids are allowed
21. Planned live vaccines within 30 days prior to the first dose of study treatment and during study treatment
22. Congenital long QT syndrome, or a corrected QTcF interval of ≥480 ms, at screening (unless secondary to pacemaker or bundle branch block).
23. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, *in situ* cervical cancer, ductal or lobular carcinoma *in situ* of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agree and document should not be exclusionary.
24. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.
25. For patients treated with camidanlumab tesirine in combination with pembrolizumab: patients intolerant to checkpoint-inhibitor or with a history of the following ≥Grade 3 immune-related adverse events: hepatitis, renal, ocular, neurologic, cardiovascular, rheumatologic, and hematologic
26. For patients treated with camidanlumab tesirine in combination with pembrolizumab: patients with a history of non-infectious pneumonitis related to prior systemic treatment and that require treatment with steroids within the last 6 months prior to enrolment.

Estimated Duration of Patient Participation and Study Duration:	The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first. The study will include a Screening Period (of up to 21 days), a Treatment Period (with cycles of 3 weeks for every 3 week [Q3W] dosing regimen), and a Follow-up Period (approximately every 12-week visits) for up to 1 year from end of treatment visit. Patients may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first. Patients benefiting clinically at 1 year may continue treatment after a case-by-case review with the Sponsor. The overall end of study occurs at the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by Sponsor.
Efficacy Assessments:	• Disease assessments: CT or MRI
Safety Assessments:	• Physical examination, including neurological examination • ECOG Performance status • Height and weight • Vital signs • Laboratory tests (hematology, chemistry, coagulation, thyroid function, urinalysis, and as applicable, additional microbiological studies) • Pregnancy test, if applicable • 12-Lead ECG (triplicate) • AEs/SAEs, graded according to CTCAE version 4.0. • DLTs (dose-escalation only)
Other Assessments:	• Blood sampling for PK, ADA, [redacted]
Study Drug, Dosage, and Mode of Administration:	Camidanlumab tesirine is administered as a 30-minute intravenous (IV) infusion on Day 1 of each cycle. Patients treated with camidanlumab tesirine as monotherapy, in the initial dose cohort will receive 20 µg/kg Q3W and the highest dose possibly tested will be 300 µg/kg Q3W. Patients treated with camidanlumab tesirine in combination with pembrolizumab, in the initial dose cohort will receive 30 µg/kg Q3W of camidanlumab tesirine. The highest dose possibly tested of camidanlumab tesirine in combination with pembrolizumab, will be the highest dose investigated and deemed safe, of camidanlumab tesirine as monotherapy. Pembrolizumab at dose of 200 mg Q3W will be administered on Day 1 of each cycle starting from Cycle 1 onwards (dosing schedule 1). If unacceptable toxicity occurs during Cycle 1, dosing Schedule 2, where pembrolizumab administration may start at Cycle 2, may be investigated in new enrolled patients.

	When given concomitantly, camidanlumab tesirine will be administered prior to pembrolizumab, and separated by 1 hour. Patients, who tolerate the combination and are in disease control, would be allowed to receive additional cycles of camidanlumab tesirine in combination with pembrolizumab, starting from Cycle 5. Additional administration of camidanlumab tesirine can be given per protocol upon informing the Sponsor. Additional administration of camidanlumab tesirine concomitantly with pembrolizumab, will be given as follow: 2 consecutive Cycles every 2 Cycles (2 Cycles on, 2 Cycles off schedule), starting from Cycle 5 for up to a year (i.e., Cycle 5 and 6, Cycle 9 and 10, Cycle 13 and 14, Cycle 17 and 18) if there is no delay in the planned treatment schedule, or, in case of delay in the administration of pembrolizumab, after respecting a minimum of 63 days (9 weeks) between the last dose of camidanlumab tesirine and the first dose of the 2 subsequent additional administrations of camidanlumab tesirine. Between these cycles, patients should receive pembrolizumab as a single agent.
Sample Size:	Approximately 95 patients; Part 1 may enroll approximately 65 patients and Part 2 will enroll approximately 30 patients.
Statistical Considerations:	Safety and tolerability analyses will be presented descriptively. ORR with 95% CI from treated patients will be presented descriptively. Duration of response, PFS, and OS will be analyzed in Kaplan-Meier approach.

SCHEDULE OF EVENTS

Table 1. Schedule of Events Every 3 Weeks (Q3W) Dosing Schedule: Camidanlumab Tesirine as Monotherapy

	Protocol Section	Screening	Treatment Period							Follow-up Period (up to 1 year from EOT)
(1 cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**				**C3 and beyond**		**EOT**	**Every 12 weeks (wks)**
Day (D)		**–21 to –1**	**1**	**3 and 5**	**8**	**15**	**1**	**8[1]**		
Informed consent	11.3	X								
Eligibility criteria	5.1 5.2	X								
Demography and Baseline Characteristics	7.2	X								
Medical/Cancer history	7.2	X								
Fresh tumor tissue collection	7.5.3.2	X prior to 1st dose (from non-target lesion)	Optional biopsy prior to C2D1 (-1 wk window)[2] and preferentially from the same site as the Baseline biopsy. This biopsy is mandatory for paired-biopsy cohorts.							
Disease assessment	7.3	X[3]	6 weeks and 12 weeks after C1D1, then every 12 wks[3]						X[3]	Every 12 wks from EOT until disease progression[4]
Physical examination, incl. neurological examination and check for infection	7.4.1	X	X		X	X	X		X	
ECOG performance status	7.4.2	X	X				X		X	
Height	7.4.3	X								
Weight	7.4.3	X	X		X	X	X	X	X	
Vital signs (BP, HR, RR, Temp)	7.4.4	X	X[6]	X	X	X	X[5]	X	X	
Hematology and Chemistry	7.4.5	X	X		X	X	X	X	X	
Coagulation and Urinalysis	7.4.5	X	X						X	
Viral detection, if applicable[6]	7.4.5	X	X				X		X	
Recommendation for VZV prophylaxis	6.10.3	For all enrolled patients								

	Protocol Section	Screening	Treatment Period							Follow-up Period (up to 1 year from EOT)
(1 cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**				**C3 and beyond**		**EOT**	**Every 12 weeks (wks)**
Day (D)		**–21 to –1**	**1**	**3 and 5**	**8**	**15**	**1**	**8[1]**		
Influenza and SARS-CoV-2	7.4.5	3-5 days or less prior to dosing on C1D1								
Pregnancy test, if applicable	7.4.6	X	On C1D1, thereafter on D1 of every other cycle						X	X[7]
12-lead ECG[8,9]	7.4.7 Table 6	X	X (Pre, EOI, Post)	X D3 only	X	X	C3 and C4 (Pre, Post), C5 (Pre), then every other cycle (Pre)		X	
Premedication	6.9.1		D-1 to D2				D-1 to D2			
Camidanlumab tesirine Administration	6.3		X				X			
PK sample[10]	7.5.1 Table 8		X (Pre, EOI, Post)	X	X	X	C3 and C4 (Pre, Post), then every cycle (Pre)		X	
ADA sample[11]	7.5.2 Table 8		X (Pre)			X C1 only	C3, C4, and C5 (Pre), then every other cycle (Pre)		X[12]	
[redacted]										
Additional microbiological studies	7.4.5	In case of suspicion of infection and GBS								
Concomitant medications	6.10	From ICF signature date or D-14, whichever is earlier, until 30 days after last dose of study drug								
Adverse events	8	AE/SAEs from ICF signature date until 30 days after last dose of study drug; thereafter, related SAEs only								

	Protocol Section	Screening	Treatment Period							Follow-up Period (up to 1 year from EOT)
(1 cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**				**C3 and beyond**		**EOT**	**Every 12 weeks (wks)**
Day (D)		**–21 to –1**	**1**	**3 and 5**	**8**	**15**	**1**	**8[1]**		
1st New anticancer treatment	4.2.3								X	X
Survival	4.2.5								X	X

Abbreviations: ADA=anti-drug antibody; AE=adverse event; BP=blood pressure; C=cycle; [redacted]; [redacted]; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; EOT=end of treatment; GBS=Guillain-Barré syndrome, [redacted]; HR=heart rate; ICF=informed consent form; iRECIST=immune-RECIST; PK=pharmacokinetic; Q3W=every three weeks; RR=respiratory rate; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; Temp=temperature; VZV=varicella zoster virus; wk=week.

1 After completion of 4 treatment cycles, the Day 8 visit is not required unless clinically indicated.

2 Timing of on-treatment biopsy and other [redacted] sample(s) may be adjusted based on emerging evidence.

3 Imaging performed within 4 weeks prior to C1D1 (beyond the screening period) can be accepted as the Screening (Baseline) assessment, and the same assessment method should be used throughout the study. Week 6 imaging should be performed within 1 week prior to C3D1 and Week 12 imaging should be performed within 1 week prior to C5D1.

All other imaging for disease assessment for patients on study drug should be performed within ±2 weeks of the scheduled timepoint. Disease assessments should be performed at the timepoints specified even if study drug dosing is delayed. If a scan has been performed within 8 weeks of EOT, it does not need to be repeated at EOT. Confirmation of progression should be performed as per iRECIST, i.e., 4 to 8 weeks after the first progressive disease assessment; if progression is not confirmed, disease assessment should continue as originally planned.

4 Disease assessments to be performed in patients having discontinued study drug for reasons other than disease progression or initiation of other anti-cancer therapy.

5 Vital signs to be measured pre, during (only BP and heart rate), and at EOI. During infusion, BP and HR will be measured every 30 minutes.

6 Serology testing for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus is mandatory at screening for patients with unknown status. Seropositive patients for or with prior history of these infections at screening will be tested during the study (not needed if seropositivity is only due to vaccination).

7 A pregnancy test should be performed ≥6.5 months after the last dose of camidanlumab tesirine.

8 Pre-dose is preferably 2 hours prior to start of infusion of camidanlumab tesirine during Cycle 1 Day 1, and within 30 minutes prior to PK sample for Cycle 2 Day 1. EOI is to be done within 10 minutes prior to EOI. Post-dose is 4 hours from the start of infusion of camidanlumab tesirine.

9 Pre-dose is within 30 minutes prior to PK sample. Post-dose is 4 hours from the start of infusion of camidanlumab tesirine.

10 Pre-dose is preferably 2 hours prior to start of infusion of camidanlumab tesirine. EOI is to be done within 5 to 10 minutes prior to EOI. Post-dose is 4 hours from the start of infusion of camidanlumab tesirine.

11 Pre-dose is within 2 hours prior to start of infusion of camidanlumab tesirine. Post-dose is 4 hours from the start of infusion of camidanlumab tesirine.

12 Patients who test positive for ADAs will be requested to supply additional ADA samples.

[redacted]

Visit Scheduling Windows:

- Treatment Period: C1D1 is the reference day, D3 and D5: visit day ± 1 day (combined D3 and D5 visit is not allowed), otherwise visit day ± 2 days
- EOT: as soon as possible after decision to discontinue the study drug, preferably within 30 days after last dose of study drug, and before initiation of any new anticancer treatment
- Follow-up Period: visit day ± 14 days

Table 2. Schedule of Events Every 3 Weeks (Q3W) Dosing Schedule: Camidanlumab Tesirine in combination with Pembrolizumab

	Protocol Section	Screening	Treatment Period							Follow-up Period up to 1 year from EOT
(1 cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**				**C3 and beyond**		**EOT**	**Every 12 weeks (wks)**
Day (D)		**–21 to –1**	**1**	**3 and 5**	**8**	**15**	**1**	**8[1]**		
Informed consent	11.3	X								
Eligibility criteria	5.1 5.2	X								
Demography and Baseline Characteristics	7.2	X								
Medical/Cancer history	7.2	X								
Fresh tumor tissue collection[2]	7.5.3.2	X prior to 1st dose (from non-target lesion)	Biopsy prior to C3D1[2] and preferentially from the same site as the Baseline biopsy.							
MMR/MSS/MSI[3]	5.1	X								
Disease assessment	7.3	X[4]	6 weeks and 12 weeks after C1D1, then every 9 wks[4]						X[3]	Every 9 wks from EOT until disease progression[5]
Physical examination, incl. skin examination, neurological examination and check for infection	7.4.1	X	X		X	X	X		X	
ECOG performance status	7.4.2	X	X				X		X	
Height	7.4.3	X								
Weight	7.4.3	X	X		X	X	X	X	X	
Vital signs (BP, HR, RR, Temp)	7.4.4	X	X (Pre, EOI)[6]	X	X	X	X (Pre, EOI)[6]	X	X	
Hematology and Chemistry	7.4.5	X	X		X	X	X	X	X	
Thyroid function test	7.4.5		X				X (Cycle 3 and every other Cycle)		X	
Coagulation and Urinalysis	7.4.5	X	X						X	
Viral detection, if applicable[7]	7.4.5	X	X				X		X	
Recommendation for VZV prophylaxis	6.10.3	For all enrolled patients								

	Protocol Section	Screening	Treatment Period							Follow-up Period up to 1 year from EOT
(1 cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**				**C3 and beyond**		**EOT**	**Every 12 weeks (wks)**
Day (D)		**–21 to –1**	**1**	**3 and 5**	**8**	**15**	**1**	**8[1]**		
Influenza and SARS-CoV-2	7.4.5	3-5 days or less prior to dosing on C1D1								
Pregnancy test, if applicable	7.4.6	X	X				X		X	X[8]
12-lead ECG	7.4.7 Table 7	X	X (Pre, EOI, Post)[9]				C3, C5 and every other Cycle (Pre)[9]		X	
Camidanlumab tesirine premedication	6.9.1		D-1 to D2				D-1 to D2[10]			
Camidanlumab tesirine Administration	6.4		X				X, starting Cycle 5[11]			
Pembrolizumab administration	6.4		X[12]				X			
PK sample[13]	7.5.1 Table 9		X (Pre, EOI, Post)	X	X	X	C3, C4, C5, C6, C7 then every other cycle (Pre)		X	
ADA sample[14]	7.5.2 Table 9		X (Pre)			X C1 only	C3, C4, C5, C6, C7 then every other cycle (Pre)		X[15]	X[15]
[redacted]										
Additional microbiological studies	7.4.5	In case of suspicion of infection and GBS								
Concomitant medications	6.10	From ICF signature date or D-14, whichever is earlier, until 30 days after last dose of study treatment								
Adverse events	8	AE/SAEs from ICF signature date until 30 days after last dose of study treatment; thereafter, related SAEs only								

	Protocol Section	Screening	Treatment Period							Follow-up Period up to 1 year from EOT
(1 cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**				**C3 and beyond**		**EOT**	**Every 12 weeks (wks)**
Day (D)		**–21 to –1**	**1**	**3 and 5**	**8**	**15**	**1**	**8[1]**		
1st New anticancer treatment	4.2.3								X	X
Survival	4.2.4								X	X

Abbreviations: ADA=anti-drug antibody; (S)AE=serious adverse event; BP=blood pressure; [redacted]; [redacted]; D=day; DESC=dose-escalation meeting committee; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; EOT=end of treatment; GBS=Guillain-Barré syndrome, [redacted]; HR=heart rate; ICF=informed consent form; MMR=mismatch repair; MSI=microsatellite instability; MSS=microsatellite stability; PK=pharmacokinetic; RR=respiratory rate; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus; Temp=temperature; VZV=varicella zoster virus; wk=week.

1 After completion of Cycle 4, the Day 8 visit is not required unless clinically indicated.

2 Timing of biopsy may be adjusted based on emerging evidence. The on-treatment biopsy should be performed between Cycle 2 Day 8 and Cycle 2 Day 15, before the disease assessment. For patients with sufficient available archival tumor tissue prior to C1D1 (biopsied after their last disease progression, and in the situation where the patient has received no anti-cancer therapy between their progression and C1D1), a fresh biopsy prior to C1D1 may not be needed. This archived tissue will be used in lieu of the fresh biopsy and the screening window will not apply to this sample obtained routinely prior to ICF signature.

3 In Dose-escalation, for patients with NSCLC or melanoma, PD-L1 expression is requested; MMR/MSS/MSI status is not required. In Dose-escalation, for patients with colorectal cancer, gastric-esophageal cancer, ovarian/fallopian tube cancer, pancreatic cancers: if MMR/MSS/MSI status is not available at signature of the informed consent, the test should be performed before C1D1. In Dose-expansion, for patients enrolled in Group 1, if MMR/MSS/MSI status is not available at signature of the informed consent, the test should be performed before C1D1. In Dose-expansion, for patients enrolled in Group 2, MSI-H/dMMR status must be available prior to ICF signature.

4 Imaging performed within 4 weeks prior to C1D1 (beyond the screening period) can be accepted as the Screening (Baseline) assessment, and the same assessment method should be used throughout the study. During the treatment period, imaging will be performed 6 weeks (42 days ±7 days) after C1D1, but prior to C3D1, and 12 weeks (84 days ±7 days) after C1D1, but prior to C5D1, then every 9 weeks (63 days ±14 days) until EOT. During the follow-up period, patients who discontinued study drug for reasons other than disease progression or initiation of other anti-cancer therapy will have imaging performed every 9 weeks (63 days ± 14 days) until 1 year from EOT. Disease assessments should be performed at the timepoints specified even if study drug dosing is delayed. If a scan has been performed within 8 weeks of EOT, it does not need to be repeated at EOT. Confirmation of progression should be performed as per iRECIST, i.e., 4 to 8 weeks after the first progressive disease assessment; if progression is not confirmed, disease assessment should continue as originally planned.

5 Disease assessments to be performed in patients having discontinued study treatment for reasons other than disease progression or initiation of other anti-cancer therapy.

6 Vital signs will be done pre-dose, at end of infusion of camidanlumab tesirine and at end of infusion of pembrolizumab.

[7] Serology testing for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus is mandatory at screening for patients with unknown status. Seropositive patients for or with prior history of these infections at screening will be tested during the study (not needed if seropositivity is only due to vaccination).

[8] A pregnancy test should be performed ≥9.5 months after the last dose of camidanlumab tesirine or ≥4 months after last dose of pembrolizumab, whichever is the latest.

[9] Pre-dose is preferably within 2 hours prior to the start of infusion of camidanlumab tesirine. EOI is within 10 minutes prior to the end of infusion of camidanlumab tesirine. Post-dose is 4 hours from the start of infusion of camidanlumab tesirine.

[10] Only when camidanlumab tesirine is administered.

[11] Additional administration of camidanlumab tesirine is allowed for patients who tolerate the combination and are in disease control after the first tumor assessment. Additional camidanlumab tesirine administration concomitantly to pembrolizumab would be given as follow: 2 consecutive Cycles every 2 Cycles, starting from Cycle 5 up to a year (i.e., Cycle 5 and 6, Cycle 9 and 10, Cycle 13 and 14, Cycle 17 and 18) if there is no delay in the planed treatment schedule, or, in case of delay in the administration of pembrolizumab, after respecting a minimum of 63 days (9 weeks) between the last dose of camidanlumab tesirine and the first dose of the 2 subsequent additional administrations of camidanlumab tesirine. Between these cycles, patients should receive pembrolizumab as a single agent.

[12] Alternative Schedules may be investigated based on observed safety and efficacy data, as assessed by the DESC: pembrolizumab from Cycle 2 onwards (Schedule 2). When administered on the same day, camidanlumab tesirine is to be administered prior to pembrolizumab separated by 1 hour (or more if clinically indicated).

[13] Pre-dose is preferably 2 hours prior to the start of infusion of camidanlumab tesirine or 2 hours prior to the start infusion of pembrolizumab, in visits without camidanlumab tesirine administration. EOI is to be done within a window of 5 minutes prior to EOI to 10 minutes after EOI. Post-dose is 4 hours from the start of infusion of camidanlumab tesirine. Collection of PK is stopped if camindanlumab tesirine administration is discontinued.

[14] Pre-dose is within 2 hours prior to the start of infusion of camidanlumab tesirine or 2 hours prior to the start infusion of pembrolizumab, in visits without camidanlumab tesirine administration. Collection of ADA is stopped if camindanlumab tesirine administration is discontinued.

[15] Patients who test positive for ADAs will be requested to supply additional ADA samples.

[redacted]

Visit Scheduling Windows:

- Treatment Period: C1D1 is the reference day, D3 and D5: visit day ± 1 day (combined D3 and D5 visit is not allowed), otherwise visit day ± 2 days
- EOT: as soon as possible after decision to discontinue the study treatment, preferably within 30 days after last dose of study treatment, and before initiation of any new anticancer treatment
- Follow-up Period: visit day ± 14 days

1 INTRODUCTION AND BACKGROUND

1.1 Targeting CD25 in Tumor Microenvironment

Advances in immunotherapies have added agents to the available armamentarium for the treatment of cancer, with novel modes of action. Some of these treatments are checkpoint inhibitors (CHPi); cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies being the "first-generation" of immune CHPi (Burugu, 2017; Wolchok, 2017; Hodi, 2010).

One of the mechanisms of anti-CTLA-4 is the activation of antitumor immunity by promoting T-cell proliferation. On the other hand, the PD-1/PD-L1 axis supports tumor immune evasion in many cancers, and blockade of this interaction using monoclonal antibodies against PD-1 or PD-L1 can lead to restoration of effector T cell (Teff) functions (Sasidharan Nair, 2018; Facciabene, 2012).

While single agent anti-CTLA-4 ipilimumab led to a response rate of around 10% in the malignant melanoma registration trial, single agent PD-1 CHPi pembrolizumab lead to an overall response rate (ORR) of >30% and single agent PD-1 CHPi nivolumab to a similar ORR at the recommended dose in a similar patient population (Johnson, 2017; Franklin, 2017; Hamid, 2017). The combination of ipilimumab with nivolumab further improved response rates and median progression free survival, but at the cost of added toxicity (Orloff, 2016). Also, in other solid tumor indications, PD-1/PD-L1 CHPi only work in about a third of patients or less as a monotherapy.

Activating effects of CHPi on CD8(+) cytotoxic T cells (in this context synonymous with Teff) are thought to be compromised by the local tumor milieu that suppresses T cell function (e.g., humoral factors such as tumor growth factor beta [TGF-β]), and CD25(+)FoxP3(+) regulatory T cells (Tregs) are known to contribute to this immunosuppressive effect (Sasidharan Nair, 2018; Tanaka, 2017).

One of the factors with particular impact on the effect of tumor eradication through the immune system is the intra-tumoral balance of Teffs versus Tregs (Sasidharan Nair, 2018; Quezada, 2008). Therefore, attempts are made to either increase the amount of CD8(+) Teffs (Bentebibel, 2017; Charych, 2016) or decrease the amount of CD25(+) Tregs. Support for the latter concept stems from publications on preclinical models (Arce Vargas, 2017) and clinical investigations (Diab, 2017; Baine, 2015; Fong, 2014). Furthermore, since CTLA-4 is expressed on Tregs, the efficacy of ipilimumab can in part be attributed to its effect on Tregs, not just on Teffs, where it is also expressed (Tanaka, 2017; Romano, 2015), lending further support to the hypothesis of achieving clinical benefit through Treg suppression. Thus, depleting or inhibiting CD25(+) Tregs may offer stand alone or additional therapeutic benefit in combination with other agents in immune-oncology, such as CHPi.

1.2 Description of Investigational Study Drug

Camidanlumab tesirine (ADCT-301) is an antibody drug conjugate (ADC), composed of the human monoclonal antibody, HuMax®-TAC, which is directed against human CD25. The antibody is conjugated through a protease cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin.

The schematic representation of camidanlumab tesirine is presented in Figure 1.

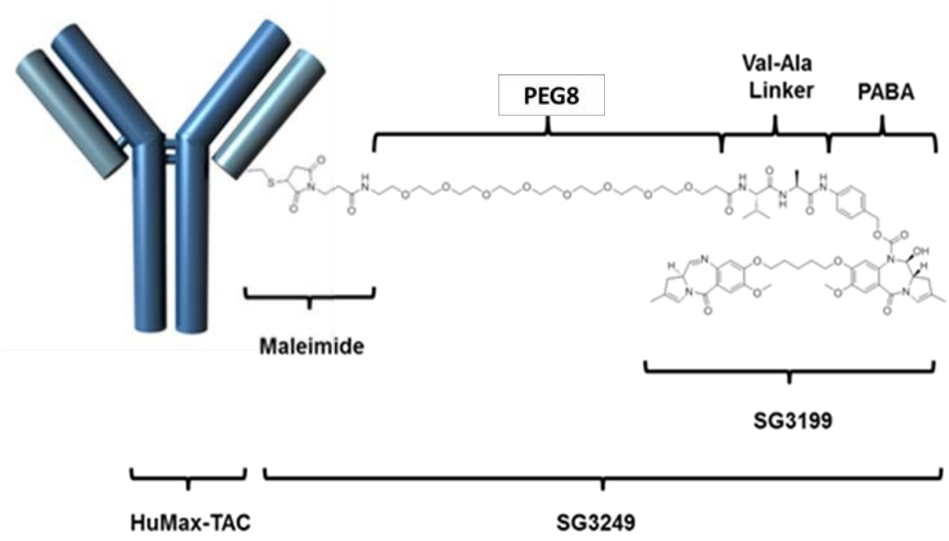


Figure 1. Schematic Representation and Chemical Structure of Camidanlumab Tesirine

Abbreviations: Ala=alanine; PABA=para-aminobenzoic acid; PEG=polyethylene glycol; HuMax-TAC=human monoclonal antibody being studied; Val, valine.

Camidanlumab tesirine binds with picomolar affinity to human CD25. After binding and internalization, camidanlumab tesirine is transported to the lysosomes, where the protease-sensitive linker is cleaved and unconjugated PBD dimers (SG3199) are released inside the target cell. The released PBD dimers bind in the minor groove of DNA in a sequence-selective manner, and form highly cytotoxic DNA interstrand cross-links. The cross-links result in a stalled DNA replication fork, blocking cell division and causing cell death (Hartley, 2011). The cross-links formed by PBD dimers are relatively non-distorting to the DNA structure, making them hidden to repair mechanisms (Adair, 2012; Beck, 2017).

1.3 Safety and Efficacy of Camidanlumab Tesirine in Clinical Studies

This is the first clinical trial of camidanlumab tesirine in solid tumors and preliminary safety and efficacy data are available; safety and efficacy data are also available from two Phase 1 studies and one Phase 2 study in hemato-oncology indications (ADCT-301-001, ADCT-301-002, and ADCT-301-201).

As of 04 Aug 2021, a total 338 patients have been treated across the entire camidanlumab tesirine monotherapy development program. There were 14 (4.2%) patients that experienced treatment-emergent Guillain-Barré syndrome (GBS)/polyradiculopathy across the entire camidanlumab tesirine development program within the 4 studies described below. This included 13 classical Hodgkin Lymphoma (cHL) subjects and one subject with non-Hodgkins lymphoma. No cases of GBS/polyradiculopathies have been observed in ADCT-301-103 at the time of the Protocol Amendment 7.

Neurologic and immune-related adverse events (AEs) including polyradiculopathy and GBS have been classified as important identified risks. Increased liver enzymes, skin toxicity (epidermal degeneration), and nephropathy have been classified as important potential risks.

Additional details may be found in the current camidanlumab tesirine (ADCT-301) Investigator's Brochure (IB).

1.3.1 ADCT-301-001

ADCT-301-001 is a first-in-human (FIH) Phase 1 dose-escalation study of camidanlumab tesirine in patients with relapsed or refractory Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), who have failed or are intolerant to established therapies, or have no other treatment options available.

ADCT-301-001 showed significant activity of camidanlumab tesirine with an acceptable safety profile in patients with HL. Anti-tumor effects have also been demonstrated in NHL patients, but the number of patients in specific sub-populations is considerably less compared to the HL population.

A total of 133 patients received at least 1 infusion of camidanlumab tesirine. Up to 150 µg/kg every 3 weeks (Q3W) was tested and the maximum tolerated dose (MTD) had not been reached.

Treatment-emergent adverse events (TEAEs) were reported in 132 out of 133 (99.2%) patients treated with camidanlumab tesirine. The most frequently reported TEAEs (≥20% overall), regardless of grade or relationship, included: fatigue (38.3%); pyrexia (32.3%); rash maculo-papular (28.6%); diarrhea (26.3%); cough and gamma glutamyl transferase (GGT) increased (22.6%); nausea (21.1%); anemia (20.3%).

Serious adverse events (SAEs), irrespective of causality, were reported in 74 (55.6%) out of 133 patients.

Out of 41 evaluable patients at the dose of 45 µg/kg Q3W, 18 (43.9%) achieved complete response (CR) and 14 (34.1%) achieved partial response (PR), for an ORR of 78.0%, as per Investigator evaluation.

1.3.2 ADCT-301-002

ADCT-301-002 is a Phase 1 dose-escalation study of camidanlumab tesirine in patients with relapsed or refractory CD25(+) acute myeloid leukemia/acute lymphoblastic leukemia, who have failed or are intolerant to established therapies, or have no other treatment options available.

A total of 35 patients received at least 1 infusion of camidanlumab tesirine in the dose-escalation portion of the study. The recommended dose for Part 2 has not been identified.

The most frequently reported TEAEs (≥20%), across dosing regimens and regardless of grade or relationship, included: fatigue (31.4%); febrile neutropenia (25.7%); decreased appetite, nausea, GGT increased and pneumonia (22.9% each); diarrhea, hypocalcemia, and pyrexia (20.0% each).

Two of the 35 patients (one each in the 30 µg/kg QW and 37.5 µg/kg QW groups) treated had a CR with incomplete hematologic recovery. All other patients had no response or progressive disease (PD).

1.3.3 ADCT-301-201

ADCT-301-201 is a multicenter, open-label, single-arm Phase 2 study in patients with relapsed or refractory HL. As of data cut-off date (26 March 2021), 117 patients have been treated. The most frequently reported TEAEs (≥20%), regardless of grade or relationship included: fatigue (36.8%), maculopapular rash (28.2%), nausea (27.4%), pyrexia (26.5%), anemia (20.5%) (Zinzani, 2021). Preliminary data are indicating that ORR was reported at 66.3% (Zinzani, 2021); data are maturing.

1.3.4 ADCT-301-103

As of 14 April 2021, enrolment in the monotherapy part was completed; 44 patients were treated with camidanlumab tesirine monotherapy in Part 1 at 8 dose levels ranging from 20 to 150 µg/kg administered on a 3-week treatment cycle and the MTD has not been reached.

The most frequently reported TEAEs (≥20% overall), regardless of grade or relationship, included: nausea (40.9%), fatigue and decreased appetite (36.4% each), constipation (29.5%), abdominal pain (27.3%), rash (22.7%). (Puzanov, 2021).

The TEAEs that have been assessed as Grade ≥3 were reported in 31 out of 44 (70.5%) patients. The most common Grade ≥3 TEAEs (observed in at least 5% of patients overall), regardless of relationship, included anemia (11.4%), abdominal pain, rash and pulmonary embolism (6.8% each).

Grade 3 autoimmune AE (colitis, immune-mediated adverse event, systemic inflammatory response syndrome) and grade 3 neurologic AE (dysphagia and asthenia), regardless of relationship, were observed in 6.8% and 4.5% of the patients, respectively.

Best overall responses were stable disease (SD) for 11 patients (25%) and progressive disease (PD) for 23 patients (52.3%); 2 patients were not evaluable (4.4%) and 8 (18.2%) had no post-baseline evaluation due to death (11.4%) or clinical progression (6.8%).

Some patients with paired biopsies showed decreased Tregs and increased Teffs:Tregs ratio in the local tumor environment, supporting a therapeutic rationale for the treatment of advanced solid tumors with camidanlumab tesirine in combination with other immune-modulating therapies (Puzanov, 2020).

At the time of this Protocol Amendment 7, the study is enrolling patients receiving camidanlumab tesirine in combination with pembrolizumab.

1.4 Pembrolizumab

Pembrolizumab is a potent, highly selective, humanized monoclonal antibody (mAb) of the immunoglobulin G 4 kappa isotype that binds to the PD-1 receptor and directly blocks the interaction between PD-1 and its ligands (PD-L1 and PD-L2), thereby enhancing tumor regression and ultimately immune rejection. Pembrolizumab has an acceptable safety profile and has been approved for treatments of patients across a number of indications.

Additional information may be found, as applicable, in the US Package Insert/EU Summary of Product Characteristics (PI/SmPC) of pembrolizumab.

1.5 Safety and Efficacy of Pembrolizumab

Most common adverse reactions (reported in ≥20% of patients) were:

- Pembrolizumab as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.
- Pembrolizumab in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis.

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab.

Pembrolizumab has been approved as single agent or in combination for the treatment of various malignancies in the US and EU including melanoma, non-small-cell lung cancer (NSCLC), head and neck squamous cell carcinoma, small cell lung cancer, classical HL, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-H, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, and renal carcinoma. The responses observed in these indications (ORR) ranged from 13% till 59%.

Additional information may be found, as applicable, in the US Package Insert/EU PI/SmPC of pembrolizumab.

2 STUDY RATIONALE

Literature evidence indicates that one of the factors with particular impact on the effect of tumor eradication through the immune system appears to be the intra-tumoral balance of Teffs versus Tregs (Section 1.1).

Sur301, a PBD dimer-based ADC directed against mouse CD25 (anti-CD25 antibody stochastically conjugated to the PBD linker drug SG3249) showed strong and durable anti-tumor activity in the MC38 and CT26 syngeneic models, two mouse colon adenocarcinoma-derived model with intra-tumoral Treg infiltration (Arce Vargas, 2017). When tested as single dose at either 0.5 or 1 mg/kg, sur301 showed complete tumor eradication in 8/8 mice at the end of the study (on Day 59). Interestingly, when a low dose of sur301 (0.1 mg/kg, single dose) was combined with an anti-PD-1 monoclonal antibody, the resulting anti-tumor activity was synergistic in both MC38 and CT26 models as shown by their coefficient of drug interaction (0.268 and 0.285, respectively) (Zammarchi, 2018; Wu, 2012). Moreover, when the tumor-free survivor animals from both studies were re-challenged with new cells, no tumors formed, indicating that the animals had developed an immunologic memory.

Targeting Tregs to enhance the efficacy of CHPi has been demonstrated to be safe, as observed in the combination of nivolumab and mogamulizumab (Doi, 2019).

Therefore, camidanlumab tesirine as a single agent or in combination with an anti-PD-1 monoclonal antibody is a candidate for targeting and selectively depleting CD25(+) Tregs in tumor infiltrates. Moreover, the intra-tumor release of camidanlumab tesirine PBD warhead may cause bystander killing of neighboring tumor cells (Flynn, 2016) and also trigger immunogenic cell death response, which will in turn strengthen the immune response against tumor cells (Rios-Doria, 2017).

2.1 Selected Tumor Types

The following tumor entities have been shown to harbor a large number of tumor-infiltrating Treg cells or for which it is known that Treg cells are involved in the tumor growth, and therefore are selected for this study (Sasidharan Nair, 2018; Tanaka, 2017): colorectal (Zhang, 2015; Hu, 2017; Scurr, 2017), head and neck squamous cell carcinoma (Schaefer, 2004), NSCLC (Wolf, 2003; Woo, 2002; Woo, 2001), gastric and esophageal cancers (Ichihara, 2003; Sasada, 2003), pancreas (Hiraoka, 2006; Tang, 2014; Jang 2017)., bladder (Parodi, 2016; Horn, 2013), renal cell carcinoma (Santagata, 2017; Asma, 2015), melanoma (Ménétrier-Caux, 2012), triple negative breast cancer (TNBC) (Plitas, 2016; Gobert, 2009; Ménétrier-Caux, 2012; Liyanage, 2002), prostate cancer (Wu, 2019), and ovarian cancer (Sato, 2005; Curiel, 2004).

In addition, indications approved for CHPi, like non-small cell lung cancer and melanoma, (Section 1.5) may also benefit from the combination of CHPi with camidanlumab tesirine, which may prime the immune system to become responsive to immunotherapy for efficiently targeting the tumor. When already exposed to checkpoint inhibitors in a prior line of treatment, Tregs may be responsible for the development of resistance (Fares, 2019) which may be overcome by treatment with camidanlumab tesirine.

2.1.1 Rationale for the Selection of Indications for the Combination in the Dose-Escalation Part

Six potential tumor indications have been selected for the dose-escalation of camidanlumab tesirine in combination with pembrolizumab: colorectal cancer, gastric/esophageal cancer, ovarian cancer, pancreatic cancer, melanoma, and NSCLC.

The first four indications listed are known to be "cold" tumors (Bonnaventura, 2019) with high unmet needs, for which immunotherapy does not show high activity (Chi, 2020; Le, 2015; Matulonis, 2019), except for the MSI-H/dMMR patients (Le, 2017; Le, 2020; Marabelle, 2019). Use of camidanlumab tesirine could help to enhance activity of CHPi in these indications by increasing the ratio Teff:Treg.

Melanoma and NSCLC are known to be "hot" tumors (Vareki, 2020), with immunotherapy already established in front-line therapy. However, most of the patients treated with an immunotherapy progressed while receiving such therapy or after the end of the immunotherapy treatment. Regulatory T lymphocytes may be involved in the acquired resistance to CHPi (Saleh, 2019). By depleting Tregs with camindanlumab tesirine, any resistance to CHPi could be overcome.

2.1.2 Rationale for the Selection of MSI-H/dMMR Patients in the Dose-Expansion

In the Dose-expansion, Group 2 will enroll patients with MSI-H/dMMR status, who have received prior CHPi therapy with best response being stable disease or better, and then progressed.

MSI-H/dMMR tumors carry hundrends to thousands of somatic mutations encoding for potential neoantigens, and can therefore be recognized by the immune system, as demonstrated by their high levels of lymphocytic infiltration, these characteristics render these tumors susceptible to reactivation of antitumor response via PD-1/PD-L1 inhibition (Dudley, 2016; Lee, 2016; Marabelle, 2019).

While, in general, MSI-H/dMMR tumors benefit from CHPi therapy, there are still between 40 to 80% patients carrying MSI-H/dMMR tumors that do not respond to anti-PD1/PD-L1 based therapies (Marabelle, 2019).

Primary and acquired resistance to anti-PD-1/PD-L1 of MSI-H/dMMR tumors can be triggered by several factors. Primary resistance in MSI-H/dMMR patients treated with PD-1/PD-L1 inhibitors could be due, among other things, to genetic factors (Sahin, 2019; Grasso, 2018; Amodio, 2021), degree of microsatellite instability impacting the insertion-deletion tumor mutational load (Mandal, 2019), lower Tumor Mutational Burden and consequent lower level of T cell infiltration in non-responders (Loupakis, 2020), as well as misdiagnosis of MSI-H/dMMR status (Cohen, 2019; Loupakis, 2020); in these patients the addition of camindanlumab tesirine is not expected to render tumors sensitive to a PD-1 inhibitor. On the other hand, the enrollment of patients that showed some degree of sensitivity to prior PD-1/PD-L1 inhibition should increase chances to select MSI-H/dMMR patients whose tumors can be recognized and attacked by the immune system, upon treatment with pembrolizumab plus camindanlumab tesirine. It is conceivable that, in at least some of these patients, the acquired resistance to prior PD-1/PD-L1 inhibitor could be due to increased Tregs infiltration and to their inhibitory activity on anti-tumor immune response. The depletion of Tregs by camindanlumab tesirine could therefore restore sensitivity to PD-1/PD-L1 inhibitors

in some of these patients, increasing the confidence that any eventual efficacy signal observed is due to the combination and not solely to pembrolizumab activity.

2.2 Rationale for Study Design

The dose-escalation portion of this study (Part 1) is designed to establish a safe and tolerated dose and dosing schedule of camidanlumab tesirine as monotherapy, and camidanlumab tesirine in combination with pembrolizumab, for further testing in patients with advanced solid tumors infiltrated by Tregs. The dose(s) and dosing schedule(s) identified in Part 1 will be tested in the dose-expansion portion of the study (Part 2) to further characterize the safety and evaluate preliminary efficacy in the study population.

Part 1 will utilize a 3+3 dose-escalation design and be under the oversight of a Dose-Escalation Steering Committee (DESC).

Part 2 will include patients who are likely to respond based on Part 1 preliminary efficacy results in order to further assess safety and tolerability of the recommended dose(s)/schedule(s).

2.3 Rationale for Dose Selection

2.3.1 Dose of Camidanlumab Tesirine as Monotherapy

Doses ranging from 3 µg/kg Q3W up to 300 µg/kg Q3W were planned to be investigated in the FIH camidanlumab tesirine clinical studies ADCT-301-001 and -002, which target CD25(+) tumors (Section 1.3); the highest dose level tested in these studies was 150 µg/kg Q3W and the MTD had not been reached. In order to minimize the dose levels to be investigated and start with a dose with potential antitumor activity, this study will investigate dose levels between 20 µg/kg and 300 µg/kg Q3W.

At the 20 µg/kg dose level, approximately 30% tumor shrinkage was observed in a HL patient (03-002) in study ADCT-301-001; lower dose levels appear to be sub-therapeutic.

Thus, 20 µg/kg Q3W has been selected as a starting dose as it represents a dose level that has previously been shown to be safe (in HL and NHL patients) and is slightly below the predicted therapeutic dose in solid tumors.

2.3.2 Dose of Camidanlumab Tesirine in combination with Pembrolizumab

Pembrolizumab dose is established at 200 mg every 3 weeks.

In the pembrolizumab/camidanlumab tesirine combination, the pembrolizumab dose will be kept constant at 200 mg; and will be combined with escalating doses of camidanlumab tesirine, in Part 1 (dose-escalation).

Clinical dose selection for camidanlumab tesirine for the combination with pembrolizumab is based on clinical efficacy and safety data from relapsed/refractory Classical Hodgkin Lymphoma (cHL) patients and patients with solid tumors. The clinical starting dose for the FIH trial (ADCT-301-001) with camidanlumab tesirine was 3 µg/kg. At 13 µg/kg a partial response was observed in a cHL patient, with lower dose levels appearing sub-therapeutic when given as a single agent. In the same trial, a 50% overall response rate was observed in cHL patients at 30 µg/kg (Collins, 2019).

In murine preclinical model, a single dose of sur301 at 0.5 mg/kg was shown to have strong and durable anti-tumor activity when used as a monotherapy. The human equivalent dose of

0.5 mg/kg is 40 µg/kg. On this trial ADCT-301-103, camidanlumab tesirine at a dose-level of 45 µg/kg, has not resulted in any responses, suggesting that the human equivalent dose calculation likely underestimates a similarly efficacious dose in human, supporting a higher starting dose compared to FIH study ADCT-301-001.

Based on the above, 30 µg/kg is the proposed starting dose for the combination with pembrolizumab. At this dose, camidanlumab tesirine is associated with a favorable clinical safety profile in solid tumor indications, whereas in cHL patients a 50% response rate and acceptable safety was observed.

In this study, investigating camidanlumab tesirine alone in advanced solid tumors patients, preliminary data of peripheral blood analyses indicate a dose related increase in CD4+ cells and to lesser extend CD8+ cells mirrored by dose dependent decrease of Treg in CD45+ lymphocyte population and leading to an increase of Teff/Treg ratio. Such immunological effects are thought to be supportive of anti-tumoral efficacy (Tanaka, 2017).

These effects are shown at dose of 30 µg/kg and above.

Camidanlumab tesirine, at the starting dose of 30 µg/kg, will be administered first for 2 cycles to perform its immunotherapy priming effect; pembrolizumab is intended to be given from the start to benefit of the potential synergistic effect seen in the non-clinical studies.

In order to minimize the dose levels to be investigated and start with a dose with potential antitumor activity, this study will investigate dose of camidanlumab tesirine in combination with pembrolizumab between 30 µg/kg and the highest dose level of camidanlumab tesirine as monotherapy shown to be safe.

A sequential dosing regimen may be implemented to mitigate overlapping toxicities at the discretion of the DESC.

3 STUDY OBJECTIVES AND ENDPOINTS

Study objectives and associated endpoints are presented below in Table 3.

Table 3. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Characterize the safety and tolerability of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab, and to identify the recommended dose(s) and schedule(s) for future studies in patients with selected advanced solid tumors	• Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab • Changes from Baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs) for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab • Frequency of dose interruptions and dose reductions for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab • Incidence of dose limiting toxicities (DLTs) (dose-escalation only) for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab
Secondary	
Evaluate the preliminary anti-tumor activity of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab	• Overall response rate (ORR) according to the Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab • Duration of response (DOR) defined as the time from the first documentation of tumor response to disease progression as per RECIST v 1.1, or death for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab • Progression-free survival (PFS) defined as the time between start of treatment and the first documentation of recurrence, progression, as per RECIST v 1.1, or death for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab • Overall survival (OS) defined as the time between the start of treatment and death from any cause for patients treated with camidanlumab tesirine as monotherapy and for patients treated with camidanlumab tesirine in combination with pembrolizumab

Objectives	Endpoints
Evaluate the pharmacokinetic (PK) profile of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab	• Concentrations and PK parameters of camidanlumab tesirine total antibody, PBD-conjugated antibody, and unconjugated warhead SG3199 in serum
Evaluate the immunogenicity of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab	• Frequency of confirmed positive anti-drug antibody (ADA) responses, their associated titers and, if applicable, neutralizing activity to camidanlumab tesirine after treatment with camidanlumab tesirine
[redacted]	

4 STUDY DESIGN

4.1 Overview

This is a Phase 1b, multi-center, open-label study with a dose-escalation part and a dose-expansion part.

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first.

The study will include a Screening Period (of up to 21 days), a Treatment Period (with cycles of 3 weeks for a Q3W dosing regimen), and a Follow-up Period (approximately every 12-week visits) for up to 1 year from End of Treatment (EOT) visit (Section 4.2).

See study diagram in Appendix 13.6.

4.1.1 Dose-Escalation

Dose-escalation cohorts:

In the dose-escalation part, patients will receive escalating doses of camidanlumab tesirine as monotherapy, or escalating doses of camidanlumab tesirine in combination with pembrolizumab, guided by a 3+3 design.

For each dose level (Section 6.3 and Section 6.4), if none of the first 3 patients at that dose level experience a DLT, new patients may be entered at the next higher dose level. If 1 of 3 patients experiences a DLT, up to 3 more patients are to be treated at that same dose level. If none of the additional 3 patients at that dose level experience a DLT, new patients may then be entered at the next higher dose level. However, if 1 or more of the additional 3 patients experiences a DLT, then no further patients are to be started at that dose level and the preceding dose is identified as the MTD. The MTD, therefore, is defined as the highest dose level at which none of the first 3 treated patients, or no more than 1 of the first 6 treated patients, experience a DLT.

If the starting dose of camidanlumab tesirine in combination with pembrolizumab is not tolerated, two lower doses could be investigated (Section 6.4). In such cases, if a DLT is observed in the first 3 patients enrolled in dose level -1, 3 additional patients will be enrolled; if 2 DLTs are observed out of these 6 patients, dose will be de-escalated to dose level -2.

Camidanlumab tesirine as monotherapy: The DLT (see Section 6.5 for further details) observation period for dose-escalation will be 21 days following the first study drug administration.

Camidanlumab tesirine in combination with pembrolizumab: The DLT (see Section 6.5 for further details) observation period for dose-escalation will start at the time of first administration of pembrolizumab and will end 21 days following this first administration of pembrolizumab.

Different dosing schedules of camidanlumab tesirine in combination with pembrolizumab may be tested in the dose-escalation part:

- Schedule 1: Administration of camidanlumab tesirine for the first 2 cycles with concomitant administration of pembrolizumab starting at the first cycle (additional administrations of camindanlumab tesirine according to a schedule with 2 cycles off – 2 cycles on, if there is no delay in the planed treatment schedule, or, in case of delay in the administration of pembrolizumab, after respecting a minimum of 63 days (9 weeks) between the last dose of camidanlumab tesirine and the first dose of the 2 subsequent additional administrations of camidanlumab tesirine; between these Cycles, patients should receive pembrolizumab as a single agent)
- Schedule 2: Administration of camidanlumab tesirine for the first 2 cycles with concomitant administration of pembrolizumab in the second cycle followed by pembrolizumab monotherapy thereafter (additional administrations of camindanlumab tesirine upon informing the Sponsor)
- The dose-escalation part will start with Schedule 1, then:
  - Schedule 2 may be initiated if dose level -1 and dose level -2 used in Schedule 1 are presenting safety concerns (e.g., significant overlapping toxicities) and investigation of Schedule 1 is stopped.
  - Other Schedules may be investigated based on observed safety and efficacy data.

No intra-patient dose-escalation is allowed in this regular dose-escalation part of the study. The number of dose levels will depend on the emergent toxicity profile of camidanlumab tesirine and will be decided by the DESC (Section 4.1.3); PK [redacted] may also inform decision making.

The DESC may expand enrollment at doses below the current dose level being evaluated as part of the dose-escalation process; additional patients, of the same indication, may only be added at dose levels that are equal or higher to the dose level for which at least 1 patient with documented PR or CR has been observed. No more than 10 patients in total can be treated at such dose level unless ≥3 of the 10 patients have documented PR or CR.

The dose-escalation part will be completed once the recommended dose(s) (and schedule[s]) for expansion (RDE)/MTD has been identified. Dose-escalation cohorts may enroll approximately 48 patients.

Paired-biopsy cohorts: Separately, paired-biopsy cohorts will enroll patients, only treated with camidanlumab tesirine as monotherapy, who will be undergoing two mandatory biopsies, one pre- and one on-treatment biopsy, [redacted]. These cohorts will be introduced at dose levels that have been deemed safe during escalation and will be composed of a maximum of 3 patients per dose level, irrespective of the indication and whether or not preliminary antitumor response(s) were seen at that dose level. In order to allow patients to benefit from trial participation, one intra-patient dose-escalation (after the mandatory on-treatment biopsy has been obtained) to the highest dose level determined to be safe at that point will be performed, unless deemed by the

Investigator not to be in the best interest of the patient. Paired-biopsy cohorts may enroll approximately up to 17 patients.

Overall, Part 1 may enroll approximately 65 patients.

4.1.2 Dose-Expansion

Two groups are planned in the dose-expansion part (Part 2):

- Group 1: an indication for which camidanlumab tesirine in combination with pembrolizumab was shown in Part 1 to have preliminary activity.
- Group 2: a basket group of patients with advanced solid tumors and MSI-H/dMMR status, who have received a prior regimen containing a PD-1/PD-L1 inhibitor, for which the best response was CR, PR, or SD ≥4 months, and then progressed while under treatment with a PD-1/PD-L1 inhibitor based regimen; no more than 4 patients with the same indication are allowed in this basket group.

Part 2 will enroll approximately 30 patients, approximately 16 patients in Group 1 and 14 in Group 2.

4.1.3 Safety Oversight by the Dose-Escalation Steering Committee

A DESC will be responsible for safety monitoring and overall supervision of the study. Membership of the DESC will include:

- Medical Monitor(s) (Sponsor and/or designee)
- Investigator(s) from each participating site
- *Ad hoc* members (e.g., project manager, study coordinator(s), regulatory representative(s), pharmacovigilance representative(s), biostatistician(s), clinical pharmacologist(s), etc.)

In general, the DESC will make any substantial decisions regarding the conduct of the study, such as:

- Monitor the safety of the study and review its progress at monthly intervals or more frequent intervals as required.
- Determine dose levels to be administered and the RDE/MTD based on assessment of safety findings in all patients and determination of DLTs in dose-escalation cohorts.
- Provide input into protocol changes, when required.
- Determine if it is appropriate to maintain a Q3W schedule or test other dosing regimens.
- Determine whether adjustment in timing of on-treatment biopsy and other [redacted] sample(s) is needed based on emerging evidence.

Each DESC meeting and the decisions made will be documented in writing and provided to all participating DESC members and Investigators. Meeting documents may be submitted to IRBs/IECs or competent authorities according to institutional or local requirements.

The DESC may be maintained during Part 2 (expansion) of the study to continue to monitor and evaluate patient safety, but the frequency of meetings can be adjusted.

4.2 Study Periods

4.2.1 Screening Period

Informed consent must be obtained for each patient and documented with a signed informed consent form (ICF) prior to any study procedures. Procedures that are performed as part of standard of care (SoC) may be used to satisfy screening requirements if they are performed in the appropriate window.

The screening period is from 21 days to 1 day prior to the start of the study drug. The screening assessments should be performed within this period in order to assess the eligibility of the patient against the inclusion and exclusion criteria (Sections 5.1 and 5.2, respectively).

See Section 5.3 for the information to be collected on screening failures.

4.2.2 Treatment Period

The treatment period starts on the date when a patient receives the first dose of study drug and continues until end of treatment visit.

A treatment cycle is defined as 3 weeks (i.e., 21 days).

After completion of Cycle 4, the Day 8 visit is not required unless clinically indicated.

Patients may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria (Section 5.4), whichever occurs first. Additionally, patients benefiting clinically at 1 year may continue treatment after a case by case review with the Sponsor.

4.2.3 End of Treatment

An EOT visit should be performed as soon as possible after the decision to discontinue the study drug, preferably within 30 days after last dose of study drug, and before initiation of any new anticancer treatment.

When EOT coincides with a scheduled visit, the scheduled visit will become EOT.

4.2.4 Follow-up Period

All patients, regardless of disease status, will be followed every 12 weeks for up to 1 year from EOT, or until withdrawal of consent, loss to follow-up, or death, whichever occurs first.

When disease assessments are not planned for a follow-up visit, the visit can be done by phone.

4.2.5 End of Study

The date of last visit/contact in the study or date of death, whichever occurs last, will be considered as the end of study (EOS) for an individual patient.

The overall end of study occurs at the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by Sponsor.

4.3 Study Stopping Rules

4.3.1 Camidanlumab Tesirine as Monotherapy

The investigation of camidanlumab tesirine as monotherapy will be stopped if any of the following circumstances occur:

- Two or more patients develop polyradiculopathy/GBS (Level 1 of diagnostic certainty; Appendix 13.2). Continuation of patients who have shown clinical benefit will be discussed with relevant regulatory authority(ies) if this stopping rule is applied.
- After 10 patients have been dosed, ≥30% of patients experience a specific Grade 4 or higher non-hematologic treatment emergent AE.

Furthermore, patient enrollment will be halted pending a safety analysis and review with the relevant regulatory authority(ies) if any patient in Part 1 or Part 2 experiences a Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 AE, or two non-hematologic CTCAE Grade 4 AEs, which are not attributable to the underlying disease, and for which relationship to camidanlumab tesirine cannot be ruled out, within 30 days of their last dose of camidanlumab tesirine.

4.3.2 Camidanlumab Tesirine in Combination with Pembrolizumab

The investigation of camidanlumab tesirine in combination with pembrolizumab will be stopped if any of the following circumstances occur:

- Two or more patients develop polyradiculopathy/GBS (Level 1 of diagnostic certainty; Appendix 13.2). Continuation of patients who have shown clinical benefit will be discussed with relevant regulatory authority(ies) if this stopping rule is applied.
- After 10 patients have been dosed, ≥30% of patients experience a specific Grade 4 or higher non-hematologic treatment emergent AE.

Furthermore, patient enrollment will be halted pending a safety analysis and review with the relevant regulatory authority(ies) if any patient in Part 1 or Part 2 experiences a CTCAE Grade 5 AE, or two non-hematologic CTCAE Grade 4 AEs, which are not attributable to the underlying disease, and for which relationship to camidanlumab tesirine or pembrolizumab cannot be ruled out, within 30 days of their last dose of camidanlumab tesirine or pembrolizumab.

5 PATIENT POPULATION

Patients must meet all inclusion criteria and none of the exclusion criteria to be eligible for the study. All criteria have to be assessed at Screening, unless otherwise specified (e.g., criterion to be confirmed within 21 days to 1 day prior to the start of study drug on Cycle 1 Day 1 [C1D1]).

5.1 Inclusion Criteria

1. Written informed consent must be obtained prior to any procedures.
2. Male or female patient aged 18 years or older.
3. Pathologic diagnosis of solid tumor malignancy that is locally advanced or metastatic at time of Screening:
   - Part 1 Dose-escalation camidanlumab tesirine as monotherapy:

     Selected advanced solid tumors: colorectal, head and neck squamous cell carcinoma, non-small cell lung cancer, gastric and esophageal cancers, pancreas, bladder, renal cell carcinoma, melanoma, triple negative breast cancer, and ovarian/fallopian tube cancer.
   - Part 1 Dose-escalation camidanlumab tesirine in combination with pembrolizumab

     Selected advanced solid tumors: colorectal cancer, gastric-esophageal cancer, ovarian/fallopian tube cancer, pancreatic cancer, non-small cell lung cancer, and melanoma.

     Note: For colorectal cancer, gastric-esophageal cancer, ovarian/fallopian tube cancer, pancreatic cancers MMR/MSS/MSI status is mandatory. If MMR/MSS/MSI status is not available at signature of the informed consent, the test should be performed before C1D1.
   - Part 2 Dose-expansion camidanlumab tesirine in combination with pembrolizumab:
     - Group 1: One of the indications identified in Part 1, for which at least 1 response (PR or CR) was seen
     - Group 2: Patients with advanced solid tumors and MSI-H/dMMR status, who have received a prior regimen containing a PD-1/PD-L1 inhibitor, for which the best response was CR, PR, or SD ≥4 months, and then progressed while under treatment with the PD-1/PD-L1 inhibitor-based regimen

       Note: A maximum of 4 patients with the same indication will be allowed in this basket group.
4. Patients who are refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.
5. Patients with advanced/metastatic cancer, with measurable disease as determined by RECIST v1.1 or immune-related Response Criteria (irRC)/ immune-related Response Evaluation Criteria In Solid Tumors (irRECIST)/ immune-related Response Evaluation Criteria In Solid Tumors (iRECIST)/ immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST) as per Investigator discretion.

Note 1: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) can be considered as measurable lesions ONLY if the soft tissue component meets the definition of measurability per RECIST.

Note 2: If immediate prior therapy contains an immuno-therapy component, progression has to meet criteria as defined in irRC/irRECIST/iRECIST/imRECIST as per Investigator discretion.

6. A) For camidanlumab tesirine as monotherapy: Patient must have a site of disease amenable to biopsy and be willing to undergo fresh biopsy procedures (minimum 3 passes each) prior to first dose, according to the treating institution's guidelines.

   B) Patients included in the paired-biopsy cohort must in addition be willing to undergo fresh biopsy procedures (minimum 3 passes each) after receiving at least 1 dose of study drug.

   C) For camidanlumab tesirine in combination with pembrolizumab: Patient must either have a site of disease amenable to biopsy and must provide fresh tumor biopsy prior to C1D1, or have sufficient available archival tumor tissue (biopsied after their last disease progression, and in the situation where the patient has received no additional anti-cancer therapy between their progression and C1D1). Patients must also be willing to undergo fresh biopsy procedures (minimum 3 passes each) after receiving at least 1 dose of study treatment, according to the treating institution's guidelines.
7. ECOG performance status 0-1.
8. Patient with life expectancy ≥3 months as per Investigator assessment.
9. Adequate organ function as defined by screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^3/\mu L$ (off growth factors at least 72 hours).
   b. Platelet count $\geq 100 \times 10^3/\mu L$ without transfusion in the past 10 days.
   c. Hemoglobin ≥9 g/dL (5.6 mmol/L) (prior transfusion allowed).
   d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma glutamyl transferase (GGT) ≤2.5 × the upper limit of normal (ULN) if there is no liver involvement; ALT or AST ≤5 × ULN if there is liver involvement.
   e. Total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 × ULN with direct bilirubin ≤1.5 × ULN).
   f. Blood creatinine ≤1.5 × ULN or calculated creatinine clearance (CL) ≥60 mL/min by the Cockcroft-Gault equation.

   Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.
10. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to start of study drug (C1D1) for women of childbearing potential (WOCBP).

11. Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 9.5 months after the last dose of camidanlumab tesirine or 4 months after last dose of pembrolizumab, whichever is the latest. Men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of giving informed consent until at least 6.5 months after the patient receives his last dose of camidanlumab tesirine or 4 months after last dose of pembrolizumab, whichever is the latest.

    * Women of childbearing potential are defined as sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

    ** Highly effective forms of birth control are methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include: hormonal contraceptives associated with inhibition of ovulation (oral, injectable, patch and intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.

    Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

5.2 Exclusion Criteria

1. Participation in another investigational interventional study.
2. Prior therapy with a CD25 (IL-2R) antibody.
3. Known history of ≥Grade 3 hypersensitivity to a therapeutic antibody.
4. Patients with prior solid organ or allogeneic bone marrow transplant.
5. History of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]) (patients with vitiligo, type 1 diabetes mellitus, residual hypothyroidism, hypophysitis due to autoimmune condition only requiring hormone replacement may be enrolled).
6. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome and myasthenia gravis) or other central nervous system (CNS) autoimmune disease (e.g., poliomyelitis, multiple sclerosis).

7. History of recent infection (within 4 weeks of C1D1) caused by a pathogen known to be associated with GBS, for example: herpes simplex virus 1/2 (HSV1, HSV2), varicella zoster (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

   Note: An influenza test and a pathogen-directed SARS-CoV-2 test (such as polymerase chain reaction [PCR]) are mandatory and must be negative before initiating study treatment (tests to be performed 3 days or less prior to dosing on C1D1; an additional 2 days are allowed in the event of logistical issues for receiving the results on time).
8. Known seropositive and requiring anti-viral therapy for human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV). Note: Testing is not mandatory to be eligible but should be considered in patients with high risk for these infections; testing is mandatory if status is unknown.
9. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.
10. Failure to recover to ≤Grade 1 (CTCAE version 4.0) from acute non-hematologic toxicity (to ≤Grade 2 for neuropathy or alopecia), due to previous therapy, prior to screening.
11. Symptomatic CNS metastases or evidence of leptomeningeal disease (brain MRI or previously documented cerebrospinal fluid [CSF] cytology). Previously treated asymptomatic CNS metastases are permitted provided that the last treatment (systemic anticancer therapy and/or local radiotherapy) was completed ≥4 weeks prior to Day 1 except usage of low dose of steroids on a taper (i.e., up to 10 mg prednisone or equivalent on Day 1 and consecutive days is permissible if being tapered down). Patients with discrete dural metastases are eligible.
12. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath).
13. Active diarrhea CTCAE Grade 2 or a medical condition associated with chronic diarrhea (such as irritable bowel syndrome, inflammatory bowel disease).
14. Active infection requiring systemic antibiotic therapy.
15. Active bleeding diathesis or significant anticoagulation (international normalized ratio [INR] ≥2.0).
16. Breastfeeding or pregnant.
17. Significant medical comorbidities, including uncontrolled hypertension (blood pressure [BP] ≥160 mmHg systolic and/or ≥110 mmHg diastolic repeatedly with or without anti-hypertensive medication), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, severe uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, active ulceration of the upper gastrointestinal (GI) tract or GI bleeding, or severe chronic pulmonary disease.

18. Major surgery, radiotherapy, chemotherapy or other anti-neoplastic therapy within 14 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor. For cytotoxic agents that have major delayed toxicity, e.g., mitomycin C and nitrosoureas, 4 weeks is indicated as washout period. For patients receiving systemic anticancer immunotherapies (as opposed to intralesional) that lead to activation of Teffs and/or increase the Teff/Treg ratio, such as anti-PD-1 antibodies, 4 weeks is indicated as the washout period.
19. Use of any other experimental medication within 14 days prior to start of study drug (C1D1).
20. Patients requiring concomitant immunosuppressive agents or chronic treatment with corticosteroids except:
    - replacement dose steroids in the setting of adrenal insufficiency
    - topical, inhaled, nasal, and ophthalmic steroids are allowed
21. Planned live vaccine within 30 days prior to the first dose of study treatment and during study treatment
22. Congenital long QT syndrome, or a corrected QTcF interval of ≥480 ms, at screening (unless secondary to pacemaker or bundle branch block).
23. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, *in situ* cervical cancer, ductal or lobular carcinoma *in situ* of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agree and document should not be exclusionary.
24. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.
25. For patients treated with camidanlumab tesirine in combination with pembrolizumab: patients intolerant to checkpoint-inhibitor or with a history of the following ≥ Grade 3 immune-related adverse events: hepatitis, renal, ocular, neurologic, cardiovascular, rheumatologic, and hematologic.
26. For patient treated with camidanlumab tesirine in combination with pembrolizumab: patients with a history of non-infectious pneumonitis related to prior systemic treatment and that require treatment with steroids within the last 6 months prior to enrolment.

5.3 Screening Failures

Patients who signed the ICF but were found not eligible for the study prior to receiving study drug are defined as screening failures.

For these patients, only limited information will be collected in the electronic case report form (eCRF):

- Informed consent
- Demographics
- Inclusion/exclusion criteria

- SAE and/or death occurring during the screening period
- Screening failure details (documenting primary reason for screen failure)

A patient who did not meet the eligibility criteria (screening failure) may be considered for re-screening. Decision for re-screening and C1D1 must be confirmed by the Sponsor/Medical monitor. A re-screened patient should be assigned a new patient number.

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

Screen failed patients could be rescreened once.

5.4 Discontinuation

The reason for discontinuation and the date of discontinuation will be collected for all patients.

Note: Once discontinued from the study for any reason, patients are not permitted to be re-enrolled.

5.4.1 Discontinuation from Study Drug

A patient may be discontinued from the study drugs for any of the following reasons:

- Disease progression (radiographic or clinical)
- Unacceptable toxicity
- Patient's decision
- Major protocol deviation
- Investigator's decision
- Discontinuation of the study by the Sponsor
- Pregnancy
- Death

IMPORTANT: Study drug discontinuation is not to be automatically considered as withdrawal from the study. Patients discontinuing the study drug will be asked to perform an EOT visit (Section 4.2.3) and continue with the Follow-up period (Section 4.2.4) as per protocol.

The investigational site should make every effort to complete follow-up per protocol. If patients are unable to return to the site, patient status (including, but not limited to, survival status) may be obtained by site staff via phone, email, or mail.

5.4.2 Discontinuation from the Study

A patient may be discontinued from the study for any of the following reasons:

- Withdrawal of consent
- Investigator/Sponsor decision
- Death

- Loss to follow-up (Section 5.4.3)
- Study completion

If a patient withdraws informed consent for study participation, no additional study data will be collected. The Sponsor may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

The study may be terminated at any time, for any reason, by the Sponsor. Patients still receiving study drug should have an EOT visit as described in Section 4.2.3 and Schedule of Events (SoE) (Table 1 and Table 2).

5.4.3 Loss to Follow-Up

Patients who fail to return for protocol follow-up are to be contacted by the investigative site. Following a minimum of two documented unsuccessful telephone calls, the investigative site should send a registered letter to the patient in a final attempt to ensure protocol compliance.

5.5 Patient Replacements

Any patient in Part 1 who discontinues before completion of the first treatment cycle, for any reason other than a DLT, is to be replaced.

6 TREATMENT

The study drugs are camidanlumab tesirine and pembrolizumab.

The study treatment refers either to camidanlumab tesirine as monotherapy or to camidanlumab tesirine in combination with pembrolizumab, as applicable.

The start of a Cycle is defined as the administration of any of the study drugs.

6.1 Study Drugs

6.1.1 Camidanlumab Tesirine

Camidanlumab tesirine will be provided as a lyophilized white to off-white powder in 2 mL glass vials (5 mg camidanlumab tesirine per vial) and stored at 2°C to 8°C. The lyophilized camidanlumab tesirine is formulated in 20 mM histidine, 175 mM sucrose, and 0.04% polysorbate 20, at pH 6.0. Prior to use, the study drug is reconstituted with 1.2 mL of sterile water for injection to deliver 1.0 mL at a concentration of 5 mg/mL. After reconstitution, the vial should be gently swirled (do not shake the vial) to ensure complete dissolution and homogeneity, and visually inspected prior to use. Sterile water for injection is to be provided by study sites. Additional study drug description is included in the pharmacy manual.

6.1.2 Pembrolizumab

Pembrolizumab will be provided as 100 mg/4 mL (25 mg/mL) liquid vial. After dilution, the liquid vial is clear to slightly opalescent, colorless to slightly yellow solution and is single-dose vial. Additional study drug description is included in the pharmacy manual.

Individual patients will receive the same formulation for their entire treatment.

6.2 Management of Clinical Supplies

Detailed instructions regarding study drug shipment, handling, storage, preparation and administration are included in the pharmacy manual.

6.2.1 Packaging and Storage

The study drug will be supplied by the Sponsor through the designated packaging, labeling, and distribution center.

All study drugs must be stored according to the pharmacy manual, in a secure area.

The lyophilized formulation of camidanlumab tesirine should be protected from long-term exposure to light and stored refrigerated at (2°C to 8°C [36°F to 46°F]).

Unopened vials of pembrolizumab liquid must be stored at 2°C to 8°C (36°F to 46°F), protected from light and must not be frozen.

Light protection is not required for dose preparation and during administration of the diluted drug in the IV bag.

6.2.2 Preparation and Administration

6.2.2.1 Camidanlumab Tesirine

The amount of the product to be diluted will depend on the dose level and the body mass of the patient. Of note, a cap on the administered dose is to be applied for patients with a body

mass index ≥35 kg/m^2; these patients will be dose based on a body mass index of 35 kg/m^2. Additional details are included in the pharmacy manual.

Administration of camidanlumab tesirine will be performed by the Investigator or a qualified designee according to the pharmacy manual.

Camidanlumab tesirine is administered as a 30-minute intravenous (IV) infusion on Day 1 of each cycle.

Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

Extravasation of camidanlumab tesirine may be associated with local irritation, swelling, pain, or tissue damage. The IV infusion site should be monitored for signs of IV infiltration or drug extravasation, and patients should be instructed to report immediately any signs of IV infiltration or drug extravasation during or after the infusion. Suspected extravasation of camidanlumab tesirine should be managed according to institutional protocol for management of extravasation of cytotoxic chemotherapy.

For patients who have a central line, administration of camidanlumab tesirine via this central line should be considered.

6.2.2.2 Pembrolizumab

Pembrolizumab will be given as a fixed dose of 200 mg administered as a 30 minutes IV infusion (starting 1 hour after the end of the camidanlumab tesirine infusion).

Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

For patients who have a central line, administration of pembrolizumab via this central line should be considered.

Please refer to prescribing information for further details, especially for monitoring of potential infusion reaction.

6.2.3 Accountability

The Investigator, or designee, will maintain accurate records of receipt of all study drugs, including dates of receipt and conditions. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. All study drugs will be reconciled and retained or destroyed according to applicable regulations.

6.3 Camidanlumab Tesirine as Monotherapy Dosing

In the dose-escalation portion of the study (Part 1), the initial dose of camidanlumab tesirine will be 20 µg/kg (Dose Level 1) every 3 weeks (Q3W), and the highest dose possibly tested will be 300 µg/kg Q3W or equivalent (e.g., 100 µg/kg every week). The dose-escalation procedure is described in Section 4.1.1.

A patient should maintain the same treatment schedule throughout the duration of the trial. However, once RDE is identified, patients receiving lower or higher dose levels of camidanlumab tesirine enrolled in Part 1 may be offered continued treatment at RDE.

Additional lower and/or intermediate dose levels to the provisional dose levels (Table 4) may be implemented. Dose level -1 may be used in case antitumor responses/significant toxicities are seen at Dose Level 1.

Table 4. Provisional Dose Levels in the Dose-Escalation (Part 1): Camidanlumab Tesirine as Monotherapy

Dose Level*	Dose of Cami
-1	10 µg/kg Q3W
1	20 µg/kg Q3W (starting dose)
2	30 µg/kg Q3W
3	45 µg/kg Q3W
4	60 µg/kg Q3W
5	80 µg/kg Q3W
6	100 µg/kg Q3W
7	125 µg/kg Q3W
8	150 µg/kg Q3W
9	200 µg/kg Q3W
10	250 µg/kg Q3W
11	300 µg/kg Q3W

* Additional or intermediate dose levels may be implemented during the study; however, the dose will not be higher than 300 µg/kg every 3 weeks (Q3W) or equivalent (e.g., 100 µg/kg every week [QW]).

Refer to Section 6.8 for premedication and supportive care.

6.4 Camidanlumab Tesirine Combination with Pembrolizumab Dosing

In the dose-escalation portion of the study (Part 1), the initial dose of camidanlumab tesirine will be 30 µg/kg (Dose Level 1) every 3 weeks (Q3W) for 2 cycles (on C1D1 and C2D1). The maximum dose possibly administered will be the highest dose of camidanlumab tesirine as monotherapy investigated and deemed to be safe. The dose-escalation procedure is described in Section 4.1.1.

Pembrolizumab at dose of 200 mg Q3W will be administered on Day 1 of each cycle starting from Cycle 1 onwards (dosing schedule 1).

If unacceptable toxicity (Section 6.5) occurs during Cycle 1 at dose level -1 and dose level -2, dosing Schedule 2, where pembrolizumab administration may start at Cycle 2, may be investigated in new enrolled patients.

Patients who tolerate the study treatment (i.e., no liver enzyme increase ≥ Grade 2, no pleural effusion ≥ Grade 2, no edema ≥ Grade 2) and are in disease control (defined as disease control ≥ SD) may receive additional doses of camidanlumab tesirine in combination with pembrolizumab, upon informing the Sponsor.

Additional administrations of camidanlumab tesirine in combination with pembrolizumab will be given as follows: 2 consecutive Cycles every 2 Cycles (2 cycles on, 2 cycles off schedule),

starting from Cycle 5 up to a year (i.e., Cycle 5 and 6, Cycle 9 and 10, Cycle 13 and 14, Cycle 17 and 18) if there is no delay in the planed treatment schedule: Between these cycles, patients should receive pembrolizumab as a single agent.

In case of delay in the administration of pembrolizumab, additional administrations of camidanlumab tesirine can be done after respecting a minimum of 63 days (9 weeks) between the last dose of camidanlumab tesirine and the first dose of the 2 subsequent additional administrations of camidanlumab tesirine.

Study treatment is given up to a year. Continued administration of camidanlumab tesirine as monotherapy or camidanlumab in combination with pembrolizumab, or pembrolizumab alone after a year is to be discussed with the Sponsor.

A patient should maintain the same treatment schedule throughout the duration of the trial. However, once RDE is identified, patients receiving lower or higher dose levels of camidanlumab tesirine enrolled in Part 1 may be offered continued treatment at RDE.

Additional lower and/or intermediate dose levels to the provisional dose levels (Table 5) may be implemented (no change in pembrolizumab dose).

If one study drug, camidanlumab tesirine or pembrolizumab, is put on hold or discontinued due to related toxicity, the other study drug could continue as single agent.

In the dose-expansion portion of the study (Part 2), patients will be assigned to the RDE of camidanlumab tesirine in combination with pembrolizumab recommended from Part 1. The RDE selected for Part 2 will be based on review of all available study data and will be recommended by the DESC.

Table 5. Provisional Dose Levels in the Dose-Escalation (Part 1): Camidanlumab Tesirine in Combination with Pembrolizumab

Dose Level*	Dose of Cami	Dose of pembrolizumab
-2	13 µg/kg Q3W × 2	200 mg Q3W
-1	20 µg/kg Q3W × 2	200 mg Q3W
1	30 µg/kg Q3W × 2 (starting dose)	200 mg Q3W
2	45 µg/kg Q3W × 2	200 mg Q3W
3	60 µg/kg Q3W × 2	200 mg Q3W
4	80 µg/kg Q3W × 2	200 mg Q3W
5	100 µg/kg Q3W × 2	200 mg Q3W
6	125 µg/kg Q3W × 2	200 mg Q3W
7	150 µg/kg Q3W × 2	200 mg Q3W
8	200 µg/kg Q3W × 2	200 mg Q3W
9	250 µg/kg Q3W × 2	200 mg Q3W
10	300 µg/kg Q3W × 2	200 mg Q3W

* Additional or intermediate dose levels may be implemented during the study; however, the dose will not be higher than the highest dose of camidanlumab tesirine as monotherapy every three weeks (Q3W) investigated and deemed safe.

6.5 Dose-Limiting Toxicities

For the dose-escalation of camidanlumab tesirine as monotherapy, a DLT is defined as any of the following events, which occur during the 21 days following the first study drug administration period of Part 1 (excluding the paired-biopsy cohorts), except those that are clearly due to underlying disease or extraneous causes.

For the dose-escalation of camidanlumab tesirine in combination with pembrolizumab, a DLT is defined as any of the following events, which occur during the 21 days following the first administration of pembrolizumab in Part 1, except those that are clearly due to underlying disease or extraneous causes.

A **hematologic** DLT is defined as:

Event	Severity
Febrile neutropenia or neutropenic infection	≥Grade 3
Neutropenia lasting >7 days	≥Grade 4
Thrombocytopenia	≥Grade 4
Thrombocytopenia with clinically significant bleeding	≥Grade 3
Thrombocytopenia requiring a platelet transfusion	≥Grade 3
Anemia	≥Grade 4
Anemia requiring transfusion	≥Grade 3

A **non-hematologic** DLT is defined as:

Event	Severity
Hy's law case	Aspartate transaminase (AST) and/or alanine transaminase (ALT) >3 × upper limit normal (ULN) and bilirubin >2 × ULN, and without initial findings of cholestasis (serum alkaline phosphatase [ALP] activity <2 × ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.
Hypersensitivity/infusion-related reaction (regardless of premedication)	≥Grade 3. A Grade 3 hypersensitivity/infusion related reaction that resolves within 24 hours after onset with appropriate clinical management does not qualify as a DLT.
Radiculitis / Polyradiculopathy / GBS	≥Grade 2
All other non-hematologic toxicity	≥Grade 3

The following conditions **are not considered** DLTs:

Event	Severity
Fatigue	Grade 3 for ≤7 days.
Diarrhea, nausea, or vomiting	Grade 3 in the absence of premedication that responds to therapy and improves by at least 1 grade within 3 days for Grade 3 events or to ≤Grade 1 within 7 days.
Alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT)	Grade 3 ALP and GGT elevations, unless considered clinically relevant by the investigator.
Serum lipase or serum amylase	Grade 3 for ≤7 days if without clinical signs or symptoms of pancreatitis.
Electrolyte abnormalities	Grade 3 that normalizes within 48 hours (with or without medical intervention) and does not manifest themselves clinically; in such instances, a follow-up sample MUST be taken within 48 hours to check whether such normalization has occurred.

A dose limiting toxicity is not a reason for treatment discontinuation.

Patients who experience a DLT that resolves or stabilizes with appropriate medical management may continue treatment at the discretion of the Investigator in consultation with the Sponsor.

6.6 Dose Delays and Modifications

When both camidanlumab tesirine and pembrolizumab have been dosed and an AE occurs with relationship to study treatment and requires study treatment hold, the resumption of study treatment can occur only with one study drug at a time. The second study drug may be resumed at the next planned Cycle.

In the above situation, prior to the resumption of any study drugs, discussion should occur with the Sponsor.

6.6.1 Dose Delays and Modifications for Camidanlumab Tesirine

The Investigator may suspend camidanlumab tesirine dosing for up to 21 days for any patient who experiences any toxicity of any grade.

Resumption of dosing with camidanlumab tesirine after any suspension, even when longer than 21 days, is at the discretion of the Investigator on assessment of the patient's clinical condition and whether or not the patient is deriving potential clinical benefit from treatment with camidanlumab tesirine.

Guidelines for management of toxicities, when considered to be at least possibly related to camidanlumab tesirine, are detailed:

- in Section 6.6.1.1 for general toxicities (i.e., not specified in the below sections),
- in Section 6.6.1.2 for specific non-hematologic toxicities,
- in Section 6.6.1.3 for specific hematologic toxicities,

- in Section 6.6.1.4 for specific neurologic toxicities,
- in Section 6.6.1.5 for specific skin toxicities.

When a patient is treated with the combination of camidanlumab tesirine and pembrolizumab, the management of irAEs related to camidanlumab tesirine will follow the recommendations for the management of irAEs related to pembrolizumab in Table 14 (Appendix 13.4).

6.6.1.1 Camidanlumab Tesirine Dose Modification Guidelines: General Toxicities

AE Grade	Camidanlumab Tesirine Management Guideline
1/2	No dose adjustment is required.
3/4	**First Occurrence:** Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline. If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, continue camidanlumab tesirine at the original assigned dose level in subsequent treatment cycles. If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, continue camidanlumab tesirine and reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. **Second Occurrence:** Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline. If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, continue camidanlumab tesirine and reduce by 2 dose levels from the original assigned dose in subsequent treatment cycles. Otherwise, camidanlumab tesirine should be permanently discontinued. **Third Occurrence:** Permanently discontinue camidanlumab tesirine.

6.6.1.2 Guidelines for Dose Modification: Specific Non-hematologic Toxicities

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
Infusion-related reactions	**1**	The infusion rate may be decreased or temporarily interrupted to permit resolution of the event. If the total time for dilution into the IV bag and infusion takes longer than 4 hours, the remaining solution of camidanlumab tesirine will be discarded and the dosing will continue with the assigned dose at the next scheduled dosing visit. Please refer to Section 6.9.4 for treatment recommendation.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
	2	Interrupt camidanlumab tesirine infusion to permit resolution of the event. If the event resolves within the total time of 4 hours after dilution into the IV bag and infusion time, resume camidanlumab tesirine infusion at 50% of the prior infusion rate, still not exceeding the total of 4 hours after infusion has restarted. If the resolution takes longer than the total 4 hours, the remaining solution of camidanlumab tesirine will be discarded, and the dosing will continue with the assigned dose at the next scheduled dosing visit at 50% of the prior infusion rate. Please refer to Section 6.9.4 for treatment recommendation.
	3	Permanently discontinue camidanlumab tesirine. However, if the AE resolves within 24 hours after onset (with or without clinical management), dosing may continue with the assigned dose at the next scheduled dosing visit at 50% of the prior infusion rate. Please refer to Section 6.9.4 for treatment recommendation.
	4	Permanently discontinue camidanlumab tesirine.
AST, ALT, or GGT abnormalities **or** **Edema** **or** **Effusion**	**2/3**	**First Occurrence:** Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline. If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, continue camidanlumab tesirine at the original assigned dose level in subsequent treatment cycles. If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, continue camidanlumab tesirine and reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. **Second Occurrence:** Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline. If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, continue camidanlumab tesirine and reduce by 2 dose levels from the original assigned dose in subsequent treatment cycles. Otherwise, camidanlumab tesirine should be permanently discontinued. **Third Occurrence:** Permanently discontinue camidanlumab tesirine.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
	4	**First Occurrence:** Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline. If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, continue camidanlumab tesirine and reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, continue camidanlumab tesirine and reduce by 2 dose levels from the original assigned dose in subsequent treatment cycles. Otherwise, camidanlumab tesirine should be permanently discontinued. **Second Occurrence:** Permanently discontinue camidanlumab tesirine.
Hy's law (AST and/or ALT > 3 × ULN and bilirubin > 2 × ULN)	**-**	Permanently discontinue camidanlumab tesirine. Hy's law defined as: AST and/or ALT >3 × ULN and bilirubin >2 × ULN, and without initial findings of cholestasis (ALP activity <2 × ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.
Autoimmune toxicities (e.g., hypothyroidism, hyperthyroidism, hepatitis, other endocrinopathies)	**≥1**	Need to be followed at least weekly to quickly detect deterioration and modify dosing as per general recommendations in Section 6.6.1.1 (can be done by telephone unless symptoms worsen). Consider using American Society of Clinical Oncology (ASCO) guidelines for management of immune mediated toxicities (Brahmer, 2018, or local guidelines). Specific guidelines for management of hyperthyroidism, hypothyroidism, and hepatitis are provided in the Appendix 13.5.
Selected Types of Infection: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, or SARS-CoV-2.	**Any Grade**	No dose adjustment is required; however, hold camidanlumab tesirine. Re-dosing must be delayed so that there is at least a 4-week window between symptom resolution and the next dose of camidanlumab tesirine. If there is suspicion that a patient may have contracted the coronavirus disease COVID-19 (e.g., recent contacts with persons who tested positive and/or recent symptoms of respiratory tract infection and/or recent loss of smell and/or taste), a pathogen-directed SARS-CoV-2 test, such as PCR, should be performed. If the patient tests positive, a repeat test should be conducted 7 to 14 days later. If the patient repeatedly tests positive without having developed symptoms, dosing may proceed at the discretion of the Investigator.

6.6.1.3 Guidelines for Dose Modification: Specific Hematologic Toxicities

Consider use of granulocyte colony stimulating factor (G-CSF) as per institutional guidelines or as per ASCO guidelines for neutropenia/febrile neutropenia. Prophylactic G-CSF may not be used during the first cycle of camidanlumab tesirine.

For anemia, consider use of erythropoietin as per institutional guidelines.

6.6.1.4 Guidelines for Dose Modification: Specific Neurologic Toxicities

Patients experiencing any new neurological toxicities and/or new onset of pain refractory to common pain medications ≥Grade 1, not explained by previous medical history, that could be linked to or may be an early indicator of polyradiculopathy/GBS, such as ascending (bilateral) sensory loss or motor weakness, need to be immediately evaluated by a neurologist and dosing of camidanlumab tesirine must be held until polyradiculopathy/GBS is ruled out. Please refer to Section 6.9.6 for management of polyradiculopathy/GBS, especially for the recommendation of prompt initiation of therapy upon reasonable suspicion of polyradiculopathy/GBS. Should further clinical, radiologic, or laboratory evidence support the diagnosis of polyradiculopathy/GBS with level 1 diagnostic certainty (Section 6.9.6 and Appendix 13.3), treatment with camidanlumab tesirine must be permanently discontinued.

Patients with ≥Grade 3 neurologic toxicities defined as peripheral sensory and peripheral motor neuropathies, and not explained by previous medical history, must have treatment with camidanlumab tesirine permanently discontinued.

Other new neurological findings not explained by previous medical history with an increase of ≥1 grade over Baseline will result in dose delay; dosing may be resumed after resolution to Baseline, at the investigator's discretion. The patient must be carefully monitored at least weekly until such resolution (can be done by telephone unless symptoms worsen).

6.6.1.5 Guidelines for Dose Modification: Specific Skin Toxicities

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
Maculopapular rash **or** **Photosensitivity rash** **or** **Pruritus**	**1**	No dose adjustment is required and monitor for change in severity. Topical treatment to affected areas is indicated: - maculopapular rash, photosensitivity rash, or pruritus: high potency topical steroid cream BID (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%). - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report).
or **Xerosis**	**2**	No dose adjustment is required and monitor for change in severity. Topical treatment to affected areas is indicated: - maculopapular rash or photosensitivity rash: high potency topical steroid cream BID (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%).

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
or **Hyperpigmentation**		- pruritus: high potency topical steroid cream BID and consider oral antipruritic (e.g., hydroxyzine, gabapentin, or pregabalin). - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report). In case these Grade 2 rashes become intolerable, Grade 3 recommendations may be applied.
	3	Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline and consider dermatology consult. Topical treatment to affected areas is indicated and consider systemic corticosteroid treatment e.g., prednisone 0.5 mg/kg for 10 days: - maculopapular rash or photosensitivity rash: high potency topical steroid cream BID (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider prednisone 0.5 mg/kg for 10 days. - pruritus: high potency topical steroid cream BID (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider oral antipruritic (e.g., hydroxyzine, gabapentin, or pregabalin). - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID; and triamcinolone 0.1% cream BID. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then: **First Occurrence:** • If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, proceed with the originally planned camidanlumab tesirine dose level. • If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. **Second Occurrence:** • If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. • If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce by 2 dose levels from the original assigned dose in subsequent treatment cycles.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
		• Otherwise, camidanlumab tesirine should be permanently discontinued. **Third Occurrence:** Permanently discontinue camidanlumab tesirine.
	4	Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline and consider dermatology consult. Topical treatment to affected areas is indicated and consider systemic corticosteroid treatment e.g., prednisone 0.5 mg/kg for 10 days: - maculopapular rash or photosensitivity rash: high potency topical steroid cream BID (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider prednisone 0.5 mg/kg for 10 days. - pruritus: high potency topical steroid cream BID (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider oral antipruritic (e.g., hydroxyzine, gabapentin, or pregabalin). - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID; and triamcinolone 0.1% cream BID. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then: **First Occurrence:** • If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, continue camidanlumab tesirine and reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. • If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce by 2 dose levels from the original assigned dose in subsequent treatment cycles. • Otherwise, camidanlumab tesirine should be permanently discontinued. **Second Occurrence:** Permanently discontinue camidanlumab tesirine.
Blistering rash	**1**	No dose adjustment is required and monitor for change in severity. Consider dermatology consult Topical treatment to affected areas is indicated, e.g., silvadene 1% cream BID and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus). Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report).

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
	2/3	Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline and consider dermatology and wound care consult. Topical treatment to affected areas is indicated, e.g., silvadene 1% cream bid, and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus) and consider systemic corticosteroid treatment e.g., prednisone 0.5 mg/kg for 10 days. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then: **First Occurrence:** • If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, proceed with the originally planned camidanlumab tesirine dose level. • If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. • Otherwise, camidanlumab tesirine should be permanently discontinued. **Second Occurrence:** • If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. • If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce by 2 dose levels from the original assigned dose in subsequent treatment cycles. • Otherwise, camidanlumab tesirine should be permanently discontinued. **Third Occurrence:** Permanently discontinue camidanlumab tesirine.
	4	Hold camidanlumab tesirine until improvement to ≤Grade 1 or Baseline and consider dermatology consult. Topical treatment to affected areas is indicated, e.g., silvadene 1% cream BID, and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus) and consider systemic corticosteroid treatment, e.g., prednisone 0.5 mg/kg for 10 days. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then:

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
		First Occurrence: • If improvement to ≤Grade 1 or Baseline occurs prior to the next scheduled dose, continue camidanlumab tesirine and reduce by 1 dose level from the original assigned dose in subsequent treatment cycles. • If improvement to ≤Grade 1 or Baseline occurs >21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce by 2 dose levels from the original assigned dose in subsequent treatment cycles. • Otherwise, camidanlumab tesirine should be permanently discontinued. **Second Occurrence:** Permanently discontinue camidanlumab tesirine.

Abbreviations: BID=twice daily; HSV=herpes simplex virus; VZV=varicella zoster virus

6.6.1.5.1 Severe Immune-Mediated Skin Adverse Events

When a patient is treated with camidanlumab tesirine in combination with pembrolizumab, and there are cases of severe immune-mediated skin adverse events related to camidanlumab tesirine, the following recommendations for camindanlumab tesirine should be followed. These recommendations align with current guidances provided in the pembrolizumab prescribing information:

- Grade 3 immune-mediated skin AE, drug reaction with eosinophilia and systemic symptoms (DRESS), suspected Stevens-Johnson syndrome (SJS), suspected toxic epidermal necrolysis (TEN): withhold treatment regimen
- Grade 4 immune-mediated skin AE, DRESS, confirmed SJS, confirmed TEN: treatment regimen permanently discontinued

6.6.1.6 Principles of Camidanlumab Tesirine Rechallenge

Exercise caution when considering resumption of camidanlumab tesirine after significant immune-related adverse events (irAEs) (≥Grade 2). Close follow-up should be performed when resuming camidanlumab tesirine to monitor recurrent symptoms:

- If re-challenged and toxicity returns, permanently discontinue camidanlumab tesirine
- Assess patient's tumor status prior to rechallenge. If an objective response (complete or partial) to camidanlumab tesirine was achieved, resumption of camidanlumab tesirine may not be advisable due to risk of toxicity recurrence. Risks/benefits of restarting camidanlumab tesirine is to be discussed with Sponsor.

6.6.2 Dose Delays and Modifications for Pembrolizumab

6.6.2.1 General rules

Dose reduction or dose-escalation are not permitted.

Management of immune-related AEs in patients treated with immune checkpoint inhibitor therapy, based on international guidelines (Brahmer, 2018; Haanen, 2017; Puzanov, 2017; NCCN, 2019) are shown in Appendix 13.4.

Guidelines for management of toxicities, when considered to be at least possibly related to pembrolizumab, are detailed in Appendix 13.4.

In the event of toxicity not relieved with optimal medical support, modifications in pembrolizumab administration include dose interruptions, delays in the start of the next cycle, and/or treatment discontinuation (refer to Section 6.6.2.2 and Appendix 13.4).

In the event of a delay in initiation of a planned Cycle of Study treatment for >21 days, the Sponsor should be contacted to discuss continuing the patient on pembrolizumab.

Pembrolizumab will be given at full dose when resumed after being held for toxicity.

If pembrolizumab is held because of AEs >12 weeks beyond the last dose, then the patient will be discontinued from pembrolizumab and will be followed for safety.

If pembrolizumab is discontinued due to significant irAE, camidanlumab tesirine could be continued, at lower dose level, after discussion with the Sponsor.

Investigators should inform Sponsor in case of immune-related AEs of any grade.

6.6.2.2 Holding Recommendations

If a patient experiences any Grade ≥3 toxicity, pembrolizumab must be held until the toxicity resolves to Grade 1 or less (Grade 1 or baseline for peripheral neuropathy).

For the dose recommendations per prescribing information, please refer to Appendix 13.4.

6.6.2.3 Principles of Pembrolizumab Rechallenge

Exercise caution when considering resumption of pembrolizumab after significant irAEs. Close follow-up should be performed when resuming pembrolizumab to monitor recurrent symptoms:

- If re-challenged and toxicity returns, permanently discontinue pembrolizumab
- Assess patient's tumor status prior to rechallenge. If an objective response (complete or partial) to pembrolizumab was achieved, resumption of pembrolizumab may not be advisable due to risk of toxicity recurrence. Risks/benefits of restarting pembrolizumab is to be discussed with Sponsor.

With some exceptions (see Appendix 13.4), resumption of pembrolizumab following Grade 2 irAEs can be considered upon resolution to ≤Grade 1.

Consult with organ-specific specialists prior to resumption of immunotherapy as appropriate following an immunotherapy hold due to irAEs. For organ-specific considerations for pembrolizumab rechallenge after a hold, refer to Appendix 13.4.

6.7 Overdose Management

For camidanlumab tesirine, the overdose is any dose given to a patient that exceeds the planned dose by 15% or more.

For pembrolizumab, an overdose is defined as any dose exceeding 5 times the prescribed dose for pembrolizumab (i.e., ≥1000 mg). No specific information is available on the treatment of overdose of pembrolizumab.

Any overdose, with or without associated AEs, drug should be held, and event must be promptly (i.e., within 24 hours after the time site personnel first learn about the event) reported to the Sponsor; in case of study treatment related AE, please refer to the dose delay and modification recommendation, listed in Section 6.6.

There are no data available to determine what the effects of overdose are and whether they can be reversed. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

If feasible, a sample for PK analysis should be taken as close as possible to the overdose event.

6.8 Treatment Compliance

Administration of the study drug will be performed by the Investigator or a qualified designee; therefore, compliance will be verified by the study drug administration information.

6.9 Premedication and Supportive Care

6.9.1 Premedication for Camidanlumab Tesirine

Unless contraindicated, administer dexamethasone 4 mg orally BID, or equivalent, the day before camidanlumab tesirine administration (if possible), the day of camidanlumab tesirine administration (give at least 2 hours prior to administration when not given the day before; otherwise any time prior to administration), and the day after camidanlumab tesirine administration.

Patients who experience an infusion-related hypersensitivity reaction will receive the alternative premedication regimen specified in Section 6.9.4.

6.9.2 Premedication for Pembrolizumab

No premedication is required for pembrolizumab.

6.9.3 Treatment of Edema and Pleural Effusion

Spironolactone at standard doses should be administered for patients with weight gain greater than 1 kg from C1D1, new or worsening edema, and/or new or worsening pleural effusion. The dose of spironolactone may be titrated as clinically indicated. Additional diuretic support may be added if there is further increase in weight, edema, or pleural effusion. Additionally, patients should be advised to monitor their weight on a daily basis, at around the same time (preferably in the morning), and to notify the study site if they gain >1 kg (2.2 pounds) over Baseline.

6.9.4 Treatment and Prophylaxis of Infusion-Related Hypersensitivity Reactions

Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, should be available for immediate use and may be administered according to site standard treatment protocols.

Any patient who experiences an infusion-related hypersensitivity reaction should receive prophylactic treatment in subsequent cycles according to the guidelines below or per institutional SoC:

- On Day 1 of each cycle, patients will be instructed to take dexamethasone 20 mg orally 12 and 6 hours before the start of the camidanlumab tesirine infusion. When necessary, 12 and 6 hours before the first infusion may be defined as "immediately before sleeping" and "immediately after waking up."
- On Day 1 of each cycle, patients will be given diphenhydramine hydrochloride 50 mg IV 30 minutes before the start of the camidanlumab tesirine infusion.
- On Day 1 of each cycle, patients will be given ranitidine (or equivalent) 50 mg IV 30 minutes before the start of the camidanlumab tesirine infusion.
- For 2 days following administration of camidanlumab tesirine on Day 1, patients are to take dexamethasone 4 mg orally BID.

6.9.5 Consideration for Skin Toxicity

6.9.5.1 Camidanlumab Tesirine

Skin toxicity has been reported in patients receiving camidanlumab tesirine for hematologic malignancies. Often, the toxicities manifested as rash were reported in sun exposed areas; it is therefore, recommended that precautions are taken to avoid exposure of skin to sunlight, even through glass (for example, use of sun protective clothing and sunglasses, sunscreen with a sun protection factor ≥30 applied every 2 hours, avoidance of being outside with no protection). Also, fragrance-free detergents and soaps are recommended.

Consideration should be given to corticosteroid therapy in patients who develop clinically significant skin toxicity (guidelines for dose modification in Section 6.6.1.5).

Photographs of skin toxicity may be taken for documentation purposes at the discretion of the Investigator provided the patient has given consent for this specific assessment.

6.9.5.2 Pembrolizumab

Immune-related severe skin reactions have been reported in patients receiving pembrolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld or permanently discontinued, and corticosteroids should be administered (see Appendix 13.4).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving pembrolizumab. For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued (see Appendix 13.4).

Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immunestimulatory anticancer agents.

6.9.6 Diagnostic, Work-up, and Management of Polyradiculopathy/ Guillain-Barré Syndrome

It is strongly recommended starting management of polyradiculopathy/GBS with either intravenous immunoglobulin (IVIg) 0.4 g/kg/day for 5 days or plasma exchange (PLEX) once diagnosis of polyradiculopathy/GBS has been considered by a neurologist; this would be at CTCAE Grade 2 symptoms for neuropathy or Score 1 as per GBS disability scale (Appendix 13.3). It has to be considered that manifestation of polyneuropathy can be variable.

Diagnostic workup should include:

- Neurology consultation
- MRI spine with and without contrast to rule out compressive lesion and evaluate for nerve root enhancement or thickening
- Electrodiagnostic studies (nerve conduction studies)
- Serologic test for SARS-CoV-2 (Alberti, 2020; Toscano, 2020; Zhao, 2020)
- Pulmonary function tests
- Lumbar puncture: CSF typically has albuminocytologic dissociation, i.e., protein elevation disproportionate to white blood cells (WBCs—although note that CSF WBCs are often elevated in GBS associated with immune checkpoint inhibitors)
- Serum antibody testing for GBS (ganglioside antibodies) when possible

Management includes:

- IVIg or PLEX as above
- If IVIg and/or PLEX do not result in improvement, consider using steroids (Gu, 2017)
- Admission to inpatient unit with capability for rapid transfer to intensive care unit-level monitoring
- Frequent focused neurological examination (at least twice daily)
- Frequent pulmonary function monitoring
- Monitoring for autonomic dysfunction
- Non-opioid management of neuropathic pain
- Treatment of constipation/ileus
- Anticoagulation
- Physical therapy

6.9.7 Other Supportive Care

Although the study patient population has a low risk for development of tumor lysis syndrome (TLS) compared to patients with acute disease (Cairo, 2010), patients should be observed for development of TLS and treated according to site standard treatment protocols.

As testing in animals showed testicular toxicity (atrophy with reduced spermatogenesis), male patients are advised to consider cryopreservation of sperm prior to treatment with camidanlumab tesirine, where applicable.

6.10 Concomitant Medications and Procedures

Medications (except for the study drug) and procedures will be recorded in the eCRF starting from the ICF signature date or from 14 days prior to C1D1, whichever is earlier, and continuing until 30 days after last dose of study drug.

6.10.1 Permitted During Study

Medications or procedures for the clinical care of the patient, including management of AEs, bisphosphonates, are permitted during the study, except for those listed in Section 6.10.2.

Hematopoietic growth factors are permitted as per ASCO guidelines (Smith, 2006). Prophylactic G-CSF may not be used during the first cycle of camidanlumab tesirine.

Local radiotherapy for analgesic/palliative purposes or for lytic lesions at risk of fracture may be carried out if required after completion of the DLT evaluation period. Whenever possible, these patients should have a tumor assessment of the lesion(s) before they receive radiotherapy to rule out progression of disease. No dose modification of study medication is needed during radiotherapy.

6.10.2 Prohibited During Study

- Other anticancer therapy during the Treatment period, with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Other investigational agents during the Treatment period.
- Live vaccines during the Treatment period and for 3 months after the last dose of study treatment

6.10.3 Varicella Zoster Virus Prophylaxis

In accordance with international guidelines related to infections in cancer patients (NCCN, 2020; Sandherr, 2006) VZV prophylaxis is recommended according to institutional guidelines for patients enrolled in this study, whether already receiving camidanlumab tesirine or newly enrolled.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Informed Consent

Informed consent, as documented by a signed and dated ICF, must be obtained prior to performing any study procedures. Results (e.g., from laboratory tests or radiographic evaluations, etc.) obtained prior to the date of informed consent but within the allowed timeframe may be used for determination of patient eligibility only if obtained as part of standard care. For additional details, please refer to Section 11.3.

7.2 Demographics and Baseline Characteristics

These assessments include:

- Demographic information such as age, gender, ethnicity, and race (to the extent allowed by local regulations).
- Cancer medical history, which includes a complete history of all surgeries and significant diagnoses, and all cancer treatment, including surgery, radiation therapy, chemotherapy, etc.
- Immune-related adverse events of prior checkpoint inhibitors
- Any other relevant medical history.
- Collection of information on prior medications used from ICF signature date or at least within 14 days prior to camidanlumab tesirine administration, whichever is earlier.
- Mutational status
    - For patients in the combination cohorts, mutational status includes as well PD-L1 expression, mismatch repair (MMR) and microsatellite stability (MSS) or microsatellite instability (MSI) status (See Section 5.1).
        - In Dose-escalation, for patients with NSCLC or melanoma, PD-L1 expression is requested; MMR/MSS/MSI status is not required.
        - In Dose-escalation, for patients with colorectal cancer, gastric-esophageal cancer, ovarian/fallopian tube cancer, pancreatic cancers: if MMR/MSS/MSI status is not available at signature of the informed consent, the test should be performed before C1D1.
        - In Dose-expansion, for patients enrolled in Group 1, if MMR/MSS/MSI status is not available at signature of the informed consent, the test should be performed before C1D1.
        - In Dose-expansion, for patients enrolled in Group 2, MSI-H/dMMR status must be available prior to ICF signature (See Section 5.1).

7.3 Efficacy Assessments

Disease assessments will occur as per SoE (Table 1 and Table 2) until progression.

Imaging performed within 4 weeks prior to C1D1 can be accepted as the Screening (Baseline) assessment.

During the treatment period, imaging will be performed 6 weeks (42 days ±7 days) after C1D1, but prior to C3D1, and 12 weeks (84 days ±7 days) after C1D1, but prior to C5D1, then every 12 weeks (84 days ±14 days) until EOT for patients treated with camidanlumab tesirine as monotherapy and every 9 weeks (63 days ±14 days) until EOT for patients treated with camidanlumab tesirine in combination with pembrolizumab.

Disease assessments should take place at the timepoints specified even if study drug dosing is delayed.

During the follow-up period, patients who discontinued study drug for reasons other than disease progression or initiation of other anti-cancer therapy will have imaging performed every 12 weeks (84 days ±14 days), for patients treated with camidanlumab tesirine as monotherapy, or every 9 weeks (63 days ±14 days) for patient treated with camidanlumab tesirine in combination with pembrolizumab, until 1 year from EOT.

If a scan has been performed within 8 weeks of EOT, it does not need to be repeated at EOT.

Additional disease assessments may be obtained, if clinically indicated.

CT or MRI scans with contrast of the chest, abdominal and pelvic area or brain scans (CT or MRI with contrast), and bone scans or X-ray exam if clinically indicated, will be performed. For image acquisition specifications, including instruction in the event of allergy to contrast dye, refer to RECIST v1.1 (Specifications for Standard Anatomical Radiological Imaging).

The same methods used at Baseline that identify sites of disease should be used uniformly for all subsequent assessments. Response to treatment will be determined by the Investigator as CR, PR, stable disease (SD), or progressive disease (PD) according to RECIST v 1.1. As per iRECIST (Seymour, 2017), the terminology “immune-” CR/PR/SD (iCR/iPR/iSD) will be used. In addition, confirmation of progression or immune-confirmed progressive disease (iCPD) should be performed as per iRECIST, i.e., 4 to 8 weeks after the first PD assessment or immune-unconfirmed progressive disease (iUPD), unless there is clear clinical deterioration which would prevent such confirmation. If progression is not confirmed, disease assessment should continue as originally planned. Clinically stable patients may at investigator discretion either interrupt or continue treatment until iCPD.

Images will be obtained according to local site imaging requirements and may be provided to Sponsor for independent review as part of comparative analysis if required.

7.4 Safety Assessments

Safety will be assessed based on the procedures in the subsection below. Adverse events/SAEs collection and reporting is described in Section 8.

Unless otherwise specified, all safety assessments on dosing days will be done prior to study drug administration.

Depending on local practice, physical examination, ECOG, and laboratory testing could be done within 24 hours before dosing.

7.4.1 Physical Examination

Physical examinations will be performed according to institutional standards and will include a whole-body skin examination.

Physical examinations will also include a neurological examination of strength, sensation, and deep tendon reflexes. Patients will be asked whether they are or have been experiencing subjective neurologic symptoms (at screening or since the last visit), such as blurred vision, muscle weakness, or paresthesia, and the response should be documented; refer to Section 6.6.1.4 for dose modification due to specific neurologic toxicities and Section 6.9.6 for details on polyradiculopathy/GBS management. This examination does not need to be conducted by a neurologist. Neurologic consultation needs to be obtained for any abnormal findings not explained by the underlying disease or previous medical history (e.g., a patient with left sided weakness known to be a result of a previous cerebrovascular accident would not need to see a neurologist as part of this study) that could be linked to or may be an early indicator of polyradiculopathy/GBS, such as ascending (bilateral) sensory loss or motor weakness, or new onset of pain, which is refractory to common pain medications with or without any additional neurological deficiencies.

The examination must include a determination if the patient has had any infection. At the discretion of the investigator, evaluation of any reported infection must be conducted to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s).

7.4.2 ECOG Performance Status

ECOG performance status grades are presented in Appendix 13.1 and will be captured as per SoE (Table 1 and Table 2).

7.4.3 Height and Weight

Height and weight will be measured as per SoE (Table 1 and Table 2).

Additional measurements will be performed if clinically indicated.

Patients should monitor their weight at home to detect potential edema/effusions. Refer to Section 6.9.3 for further details.

7.4.4 Vital Signs

Vital signs will be measured as per SoE (Table 1 and Table 2).

Vital signs include the measurements of arterial BP (systolic and diastolic), heart rate, respiratory rate, and body temperature and will be performed according to the institutional standards.

For Day 1 of each cycle, vital signs are to be measured before the start of the camidanlumab tesirine infusion, and at the end of infusion (example in Figure 2).

For patients treated with pembrolizumab, vital signs will be also collected at the end of infusion of pembrolizumab.

7.4.5 Laboratory Tests

Samples will be collected at the time points specified as per SoE (Table 1 and Table 2) and will be analyzed locally. Additional sample(s) may be collected and analyzed if clinically indicated. The C1D1 laboratory test(s) can be waived if the laboratory test(s) for eligibility was done within 3 days of C1D1.

Hematology: WBCs with 5-part differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, hemoglobin, and hematocrit.

Chemistry: ALT, AST, GGT, ALP, amylase, lipase, total bilirubin (conjugated and unconjugated bilirubin only when total bilirubin is abnormal), sodium, potassium, chloride, phosphate/phosphorus, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, creatinine, creatine phosphokinase, total protein, albumin, glucose, and lactate dehydrogenase.

Coagulation: partial thromboplastin time (PTT)/activated PTT (aPTT) and INR (prothrombin time to be collected if INR is not available).

Thyroid function: Thyroid-Stimulating Hormone (TSH); reflex free T4 and/or free T3, as applicable, only when TSH is abnormal.

Urinalysis: pH, specific gravity, protein, WBCs, red blood cell (RBCs), ketones, glucose, and bilirubin.

Urinalysis may be performed by dipstick. Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation consists at a minimum of WBC and RBC quantitation per high power field, as well as semi-quantitative assessment of other cells and substances, if present, such as epithelial cells, bacteria, and crystals ("few", "moderate,", "many"). Other evaluations depending on microscopic findings may be added.

Viral detection: Seropositive patients for, or with prior history of, HIV, HBV, or HCV not receiving antiviral therapy at screening will be monitored during the study (not needed if seropositivity is only due to vaccination).

Influenza and SARS-CoV-2: An influenza test and a pathogen-directed SARS-CoV-2 test (such as PCR) must be performed and be negative for eligibility purposes.

Additional microbiological studies: Pathogens of interest are: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, or SARS-CoV-2.

Patients will be regularly examined and asked whether they have been suffering from or exhibit symptoms of an infection during their participation in the trial. If there is a reasonable suspicion that such infection could have been caused by one of the pathogens listed above, appropriate microbiological workup should be conducted, provided the availability of the test(s). See Section 6.6.1.2 for dose delay recommendation upon confirmation of infection by one of these microorganisms.

If there is suspicion that a patient may have contracted the coronavirus disease COVID-19 (e.g., recent contacts with persons who tested positive and/or recent symptoms of respiratory tract infection and/or recent loss of smell and/or taste), a pathogen-directed SARS-CoV-2 test, such as PCR, should be performed. If the patient tests positive, a repeat test should be conducted 7 to 14 days later. If the patient repeatedly tests positive without having developed symptoms, dosing may proceed at the discretion of the Investigator.

7.4.6 Pregnancy Test

A highly sensitive β-HCG test in urine or blood β-HCG test will be performed in WOCBP for eligibility (see Section 5.1) and throughout the study as per SoE.

The C1D1 pre-dose pregnancy test can be waived if the test for eligibility was done within 7 days of C1D1. After starting the study drug, all efforts should be made to keep the interval between two consecutive pregnancy tests no more than 6 weeks.

If a pregnancy test is positive, the study drug must be held pending confirmation. If the pregnancy is confirmed, study treatment will be discontinued permanently for the patient. Refer to Section 8.6 for the handling of the patient and reporting the event.

A pregnancy test is to be performed at the EOT visit. In addition, a pregnancy test should be performed ≥9.5 months after the last dose of camidanlumab tesirine (i.e., end of relevant systemic exposure considering 5 half-lives plus 6 months for other than aneugenic genotoxic compound [CTFG, 2020; FDA, 2019] or ≥4 months after the last dose of pembrolizumab, whichever is the latest. The patient will be asked either to come back to the site for a pregnancy test or she will be given a prescription for a pregnancy test. The result will be collected over the phone or will be faxed/emailed to the site. The contact with the patient and the result of the pregnancy test must be documented on source documents at the site.

7.4.7 ECG

Three consecutive (also called triplicate) 12-lead ECGs will be performed at defined timepoints throughout the study as per SoE (Table 1 and Table 2). Refer to Table 6 for the detailed schedule of ECGs, for patients treated with camidanlumab tesirine as monotherapy.

Refer to Table 7 for the detailed schedule of ECGs, for patients treated with camidanlumab tesirine in combination with pembrolizumab.

ECGs will be performed after the patient has rested for at least 5 minutes.

At timepoints coinciding with blood sample collection, including PK, ECGs should be taken prior to blood collection, and, when applicable, before vital signs measurements (example in Figure 2).

If a patient experiences Torsade de Pointes, additional concomitant PK samples (i.e., unscheduled) should be collected.

Table 6. Schedule for Triplicate ECG Collection (Q3W Schedule): Camidanlumab Tesirine as Monotherapy

Cycle	Day	ECG timepoint (window)
Screening	-	Any time within 21 days prior to C1D1
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI) Post-dose* 4 h (± 15 min)
	D3	Post-dose* 48 h (± 24 h; but within 30 min prior to PK sample)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 48 h; but within 30 min prior to PK sample)
C2	D1	Pre-dose (within 30 min prior to PK sample) EOI (within 10 min prior to EOI) Post-dose* 4 h (± 15 min)
	D3	Post-dose* 48 h (± 24 h; but within 30 min prior to PK sample)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 48 h; but within 30 min prior to PK sample)
C3 and C4	D1	Pre-dose (within 30 min prior to PK sample) Post-dose* 4 h (± 15 min)
C5, C7 every other cycle	D1	Pre-dose (within 30 min prior to PK sample)
EOT		Any time (but within 30 min prior to PK sample)
Unscheduled		Any time

Abbreviations: C=cycle; D=day; ECG=electrocardiogram; EOI=end of infusion; EOT=end of treatment; h=hour; min=minutes; PK=pharmacokinetics; Q3W=every 3 weeks.
* Post-dose timepoint is counted from start of infusion.

Table 7. Schedule for Triplicate ECG Collection (Q3W Schedule): Camidanlumab Tesirine in combination with Pembrolizumab

Cycle	Day	ECG timepoint (window)
Screening	-	Any time within 21 days prior to C1D1
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI of camidanlumab tesirine) Post-dose* 4 h (± 15 min)
C2	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI camidanlumab tesirine) Post-dose* 4 h (± 15 min)
C3, C5, every other Cycle	D1	Pre-dose (preferably within 2 h prior to start of infusion)
EOT		Any time (but within 30 min prior to PK sample)
Unscheduled		Any time

Abbreviations: C=cycle; D=day; ECG=electrocardiogram; EOI=end of infusion; EOT=end of treatment; h=hour; min=minutes; PK=pharmacokinetics; Q3W=every 3 weeks.
* Post-dose timepoint is counted from start of infusion of camidanlumab tesirine

Electrocardiograms will be submitted for a central review; however, local ECG results may be used for patient eligibility or medical decisions when central results are not received in a timely manner.

Submission instructions for the central review will be provided in a separate manual. Assessments will include determination of heart rate and rhythm and the PR, QRS, QT, QTcF, and QTcB intervals.

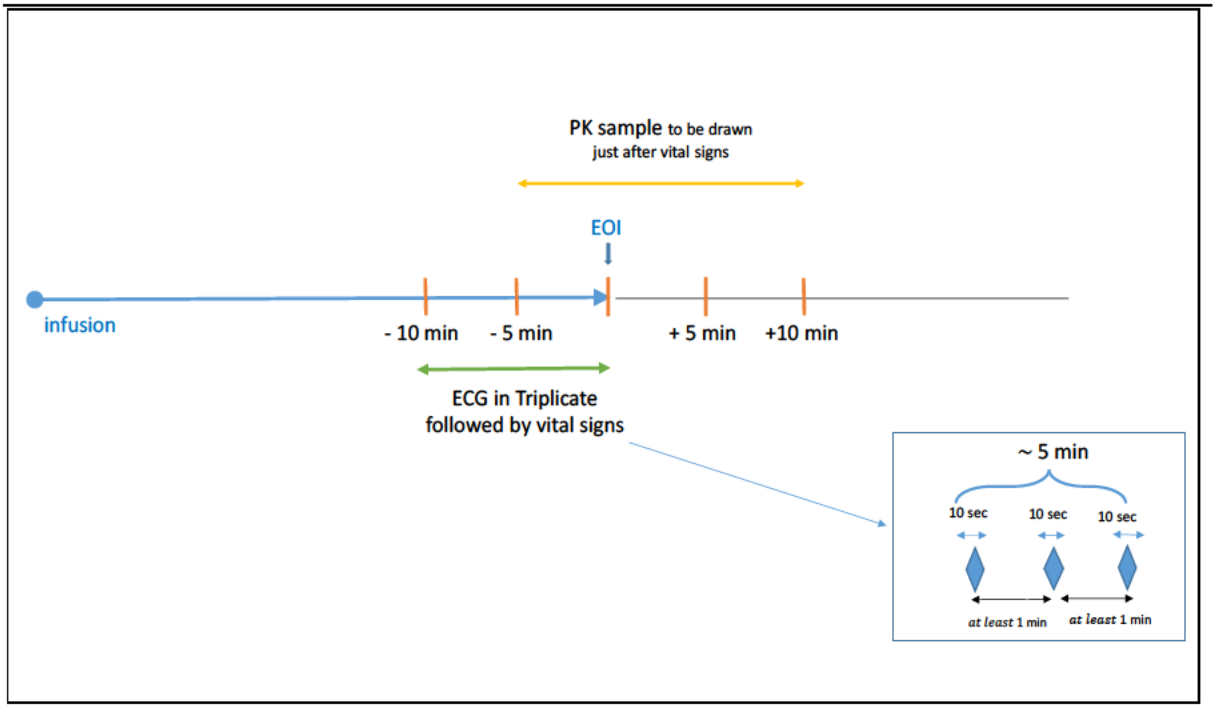


Figure 2. Preferred Sequence for Triplicate ECG, Vital Signs, and PK Sample Assessments at End of Infusion (EOI)

7.5 Pharmacokinetics [redacted] and Immunogenicity

Pharmacokinetics, ADA, [redacted] samples will be collected as per SoE (Table 1 and Table 2).

Additional biological samples may be collected by the Investigator when clinically indicated (e.g., at the time of significant AEs that are at least possibly related to the study drug) and may be used for PK, [redacted] testing.

When multiple samples are required at the same timepoint, collection of safety samples should be first, followed by PK, then [redacted]

In order to better understand the disease, metabolic disposition, and pharmacologic behavior of camidanlumab tesirine as monotherapy and camidanlumab tesirine in combination with pembrolizumab in humans, samples remaining after primary analyses may be utilized for further analysis.

Biological samples may be retained for up to 10 years to further address scientific questions as new information in regard to the disease or the study drug becomes available.

For detailed instructions related to central laboratory sample collection, labeling, processing, storage, or shipment refer to the appropriate laboratory manual(s).

7.5.1 Pharmacokinetics

The PK profile of camidanlumab tesirine PBD-conjugated antibody, total antibody, and unconjugated warhead SG3199 will be assessed in serum by a central laboratory designated by the Sponsor using validated bioanalytical methods.

Up to 6 mL of whole blood will be collected as per Table 1 and Table 8 for the patients treated with camidanlumab tesirine as monotherapy, as per Table 2 and Table 9 for the patients treated with camidanlumab tesirine in combination with pembrolizumab.

Blood should be drawn from a vein away from the one used for study drug infusion.

The serum PK samples must be stored at ≤ -70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

At timepoints coinciding with ECG collection, PK blood collection should occur immediately after the end of the ECG recording and, when applicable, after vital signs (example in Figure 2). If a patient experiences Torsade de Pointes, concomitant PK samples (e.g., unscheduled) should be collected.

Table 8. Sampling Schedule for PK and ADA (Q3W Schedule): Camidanlumab Tesirine as Monotherapy

Cycle	Day	PK timepoint (window)	ADA timepoint (window)
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion of camidanlumab tesirine) EOI of camidanlumab tesirine (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (preferably within 2 h prior to start of infusion of camidanlumab tesirine)
	D3	Post-dose* 48 h (± 24 h)	-
	D5	Post-dose* 96 h (± 24 h)	-
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	Post-dose* 336 h (± 48 h)
C2	D1	Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine) EOI of camidanlumab tesirine (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine)
	D3	Post-dose* 48 h (± 24 h)	-
	D5	Post-dose* 96 h (± 24 h)	-
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	-
C3 and C4	D1	Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine) Post-dose* 4 h (± 10 min)	Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine)
C5, C6, C7, every cycle	D1	Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine)	
C5, C7, every other cycle	D1		Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine)
EOT		At any time during visit day	At any time during visit day
Unscheduled		Any time	Any time (if applicable, together with PK sample)

Abbreviations: ADA=anti-drug antibody; C=cycle; D=day; EOI=end of infusion; EOT=end of treatment; h=hour; min=minutes; PK=pharmacokinetics; Q3W=every 3 weeks.

* Post-dose timepoint is counted from start of infusion of camidanlumab tesirine.

Table 9. Sampling Schedule for PK and ADA (Q3W Schedule): Camidanlumab Tesirine in combination with Pembrolizumab

Cycle	Day	PK timepoint (window)[1]	ADA timepoint (window)[1]
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion of camidanlumab tesirine) EOI of camidanlumab tesirine (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (preferably within 2 h prior to start of infusion of camidanlumab tesirine)
	D3	Post-dose* 48 h (± 24 h)	-
	D5	Post-dose* 96 h (± 24 h)	-
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	Post-dose* 336 h (± 48 h)
C2	D1	Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine) EOI of camidanlumab tesirine (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (within 2 h prior to start of infusion of camidanlumab tesirine)
	D3	Post-dose* 48 h (± 24 h)	-
	D5	Post-dose* 96 h (± 24 h)	-
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	-
C3, C4, C5, C6, C7 then every other Cycle	D1	Pre-dose (within 2 h prior to start of infusion of study treatment)	Pre-dose (within 2 h prior to start of infusion of study treatment)
EOT		At any time during visit day	At any time during visit day
Unscheduled		Any time	Any time (if applicable, together with PK sample)

Abbreviations: ADA=anti-drug antibody; C=cycle; D=day; EOI=end of infusion; EOT=end of treatment; h=hour; min=minutes; PK=pharmacokinetics; Q3W=every 3 weeks.

* Post-dose timepoint is counted from start of infusion of camidanlumab tesirine.

[1] Upon consultation with the Sponsor, PK and ADA samples will not be collected anymore if camidanlumab tesirine is permanently discontinued and pembrolizumab continues as single agent.

For patients treated with camidanlumab tesirine in combination with pembrolizumab, the collection of PK data will be stopped upon consultation with the Sponsor if camidanlumab tesirine administration is discontinued and pembrolizumab continues.

To understand the metabolic disposition of camidanlumab tesirine in humans, samples remaining after PK analysis is complete may be pooled among patients for potential metabolite identification.

7.5.2 Immunogenicity

Detection of ADAs against camidanlumab tesirine will be performed by using a screening assay for identification of antibody positive samples/patients, a confirmation assay, and titer assessment.

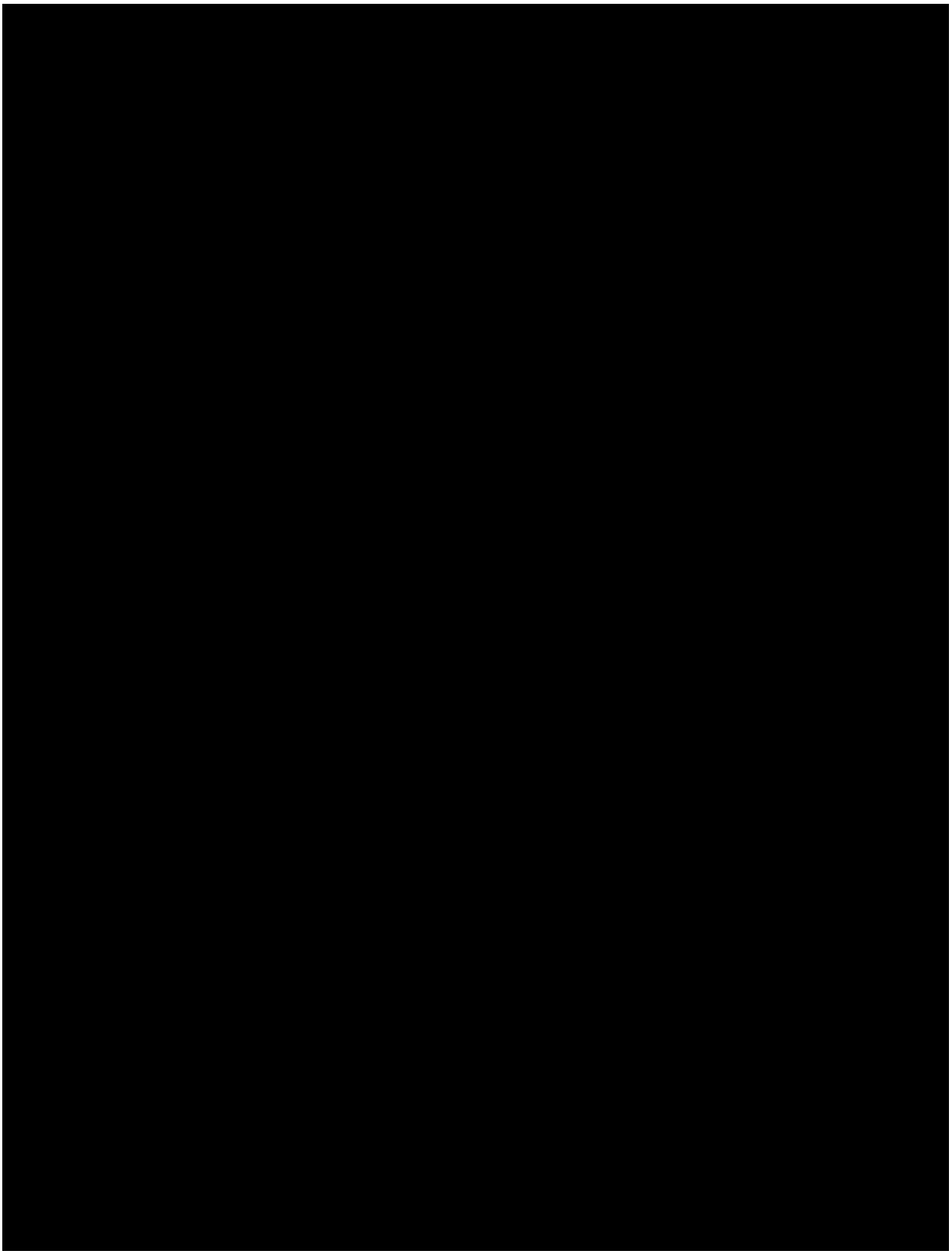
Up to 6 mL of whole blood will be collected as per Table 1 and Table 8 for the patients treated with camidanlumab tesirine as monotherapy, as per Table 2 and Table 9 for the patients treated with camidanlumab tesirine in combination with pembrolizumab.

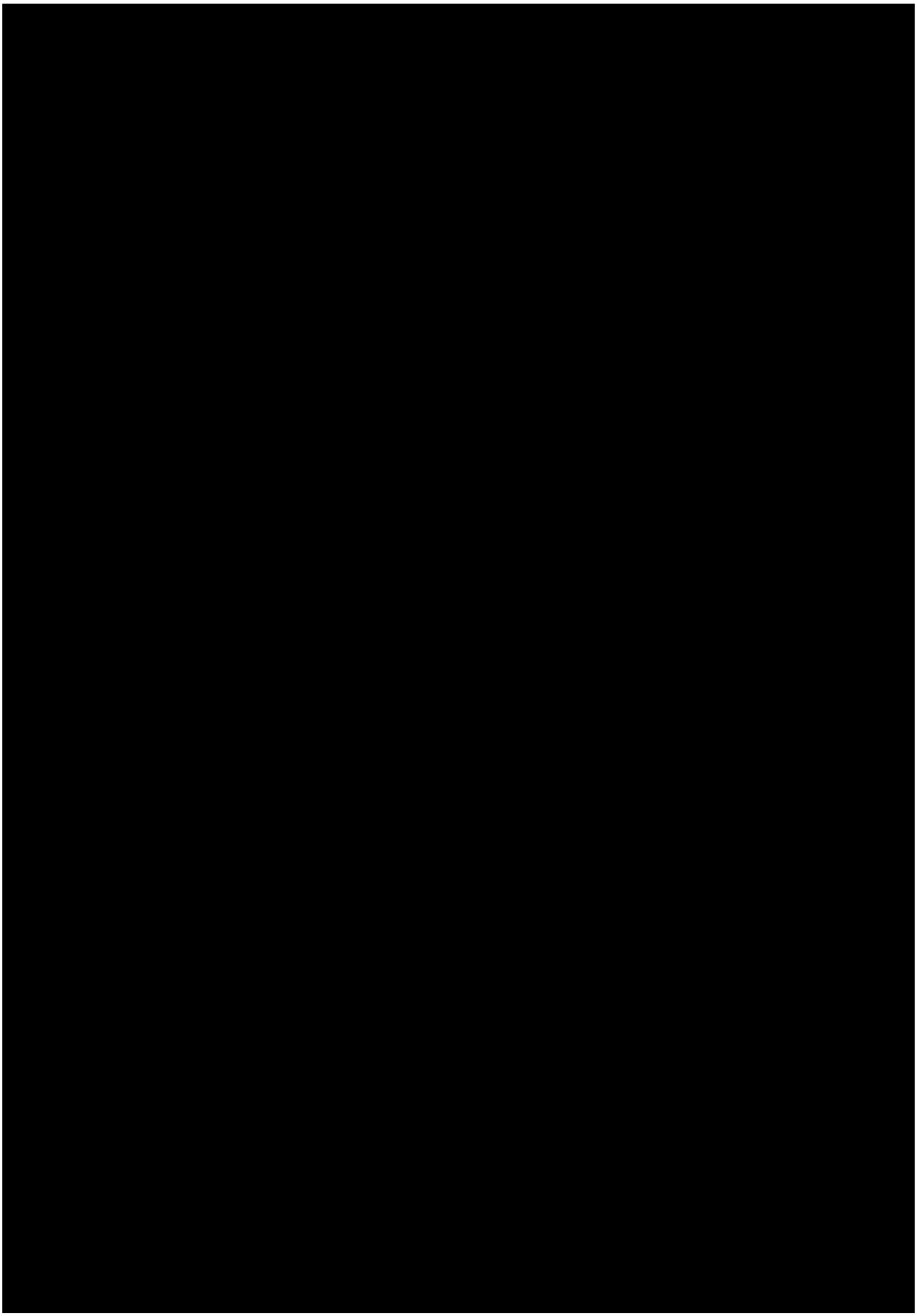
Blood should be drawn from a vein away from the one used for study drug infusion.

For patients who test positive for ADA, additional ADA samples will be requested for testing every 12 weeks following the EOT visit until the ADA titer falls to a background level, as long as the patient is still on-study.

The ADA samples must be stored at ≤ -70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

For patients treated with camidanlumab tesirine in combination with pembrolizumab, unless there is a penultimate observation of positive ADA response, no other collection of ADA data is necessary if camindanlumab tesirine administration is discontinued.





8 ADVERSE EVENTS

8.1 Definition of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment.

Test results collected during the study (e.g., laboratory values, physical examinations, ECGs, etc.) or identified from review of other documents may constitute AEs if deemed clinically significant.

An SAE is defined as any AE that:

- results in death.
- is life threatening.
- requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization for elective procedures or for protocol compliance is not considered an SAE).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- important medical events that do not meet the preceding criteria but based on appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed above.

Adverse Events of Special Interest (AESIs) are significant AEs that are judged to be of special interest because of clinical importance, known class effects, or based on preclinical signals. Events considered to be AESIs are identified in Section 8.1.1.

8.1.1 Adverse Events of Special Interest

For this study the following AEs, irrespective of seriousness and causality, are considered AESIs (except those clearly attributed to pembrolizumab alone):

- GBS (including variants such as acute motor and sensory axonal neuropathy)
- Polyradiculopathy
- Autonomic nervous system imbalance
- Nerve palsy
- ≥Grade 3 neurologic toxicities
- ≥Grade 3 immune-mediated toxicities. Of note, rashes will not be considered as immune-mediated skin toxicities, since they are well described toxicities of PBD-dimers; with exception for Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, exfoliative dermatitis, and drug reaction with eosinophilia and systemic symptoms (Note: immune-mediated skin toxicities will need confirmatory skin biopsy)

- Autoimmune-mediated events (such as, but not limited to, pneumonitis, hepatitis, colitis, endocrinopathies, type 1 diabetes mellitus, and nephritis/renal dysfunction)

For all AESIs it is important to provide as much information as possible: e.g., time of onset (including changes in severity), duration of events, time to resolution, and relationship to camidanlumab tesirine. It is also important to specify if any AEs are autoimmune mediated.

Adverse events of special interest will be closely monitored and followed.

8.2 Eliciting and Reporting Adverse Events/Adverse Events of Special Interest/Serious Adverse Events

Patients will be instructed to contact the Investigator at any time after ICF signature if any symptoms develop. At each study visit, patients will be asked a non-leading question to elicit any medically related changes in their well-being. Patients may also report AEs voluntarily and they will be instructed to contact the Investigator between visits if any symptoms develop or worsen.

All AEs will be reported starting when the patient provides written informed consent. Clinically significant medical conditions present at the time of ICF signature will be reported as medical history. Clinically significant medical conditions that start or worsen after ICF signature will be reported as AEs.

All AEs, AESIs, and SAEs, regardless of relationship to study drugs (camidanlumab tesirine and pembrolizumab), will be reported from the time the patient signs the ICF until 30 days after the last dose of study drug; thereafter, only related SAEs will be reported.

Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If no diagnosis is available or has been identified, then the primary symptom is reported.

In general, the term ‘disease progression’ should not be used for reporting an AE/SAE. However, AEs/SAEs that are complications of disease progression should be reported.

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected will include event term, date of onset, assessment of severity (Section 8.3), seriousness (Section 8.1), relationship to study drug (Section 8.4), action taken with study drug, date of resolution of the event or ongoing (when no resolution by the end of the reporting period), any required treatment or evaluations, and outcome.

New serious AESIs/SAEs and any recurrent episodes, progression, or complications of the original serious AESI/SAE must be reported to the pharmacovigilance department of the Sponsor or delegate (e.g., contract research organization [CRO]) within 24 hours after the time site personnel first learn about the event. Reporting will occur through the electronic data capture (EDC) system.

Any recurrence of GBS/polyradiculopathy, irrespective of the relationship to study drug, has to be reported to the Sponsor, including when the recurrence occurs when the patient has already completed the study. The reporting of such events after the patient has completed the study will be captured via the Sponsor’s safety database and therefore will not impact database lock.

Non-serious AESIs must be entered in the EDC system and reported to the Sponsor or delegate (e.g., CRO) within 48 hours after the time site personnel first learn about the event.

8.3 Assessment of Severity

All AEs will be graded according to CTCAE version 4.0. For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5 as shown in Table 12.

Table 12. Definition of Severity Grades for Common Terminology Criteria for Adverse Events

Grade	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)[a].
3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

[a] ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The AEs characterized as intermittent do not require documentation of onset and duration of each episode.

8.4 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is an important part of safety reporting but is not a factor in determining whether an AE is reported. An AE will be assessed as related to study drug if there is a reasonable possibility of causal relationship with the use of the study drug. For SAEs, whenever possible, the Investigator should provide a rationale for the causality assessment.

8.5 Regulatory Reporting

Reporting of AEs to competent authorities and independent ethics committees (IECs) will be consistent with local laws, regulations, guidelines, and requests.

8.6 Pregnancy Reporting

Any pregnancy in a participant that occurs from signing the ICF up to 9.5 months after the last dose of camidanlumab tesirine, or up to 4 months after the last dose of pembrolizumab, whichever is the latest, must be reported using the Pregnancy Report Form. Any pregnancy in a partner of a male patient that occurs from signing the ICF up to 6.5 months after the last dose of camidanlumab tesirine, or up to 4 months after the last dose of pembrolizumab, whichever is the latest, must be reported. Pregnancy must be reported within 24 hours after the site personnel first learn of the pregnancy. The pregnancy itself is not considered an AE. However, the pregnancy must be followed to determine outcome (including spontaneous

miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient discontinued from the study. Abortions (elective or spontaneous) must be reported as an SAE.

Any SAE occurring in association with a pregnancy that is brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study drug must be promptly reported in the same manner.

Once pregnancy is confirmed in a study participant, study drug will be discontinued; see Section 7.4.6 for additional information.

9 STATISTICAL CONSIDERATIONS

Full details of the analysis plan, including a more technical and detailed elaboration of the statistical analyses, will be provided in the statistical analysis plan (SAP). [redacted]

9.1 Sample Size Calculation

Approximately 95 patients; Part 1 may enroll approximately 65 patients and Part 2 will enroll approximately 30 patients, approximately 16 patients in Group 1 and 14 in Group 2.

9.2 Analysis Populations

- The Safety analysis set consists of all patients who receive study drug
- The DLT-evaluable analysis set consists of patients in Part 1 who receive study drug: However, this set excludes:
  - Patients in Part 1 who discontinue from the study during the DLT period (see Section 6.5) without experiencing a DLT
  - Patients in Part 1 enrolled in the paired-biopsy cohort
  - Additional patients in Part 1, of same indication, enrolled at a dose level equal or higher to the dose level for which at least 1 patient with documented PR or CR has been observed
- The Efficacy analysis set will consist of all patients who receive at least 1 dose of study drug (refer to Section 6), have valid Baseline disease assessment(s), and at least one valid post-Baseline disease assessment. Patients who do not have a post-Baseline assessment due to early clinical progression or death (after receiving study drug) will also be included.
- The PK analysis set consists of all patients who receive study drug and have at least 1 pre-(C1D1) and 1 post-dose valid assessment.
- [redacted]

9.3 Interim Analysis

No formal interim analysis is planned.

9.4 Final Analysis

All efficacy and safety endpoints will be analyzed and reported in the clinical study report (CSR).

9.5 Demographics and Baseline Characteristics

Demographics and Baseline characteristics, such as cancer history and medications history, will be summarized for the Safety analysis set by dose level.

9.6 Exposure to Treatments

Exposure to study drug, prior, and concomitant medications will be summarized for the Safety analysis set by dose level. Dose interruptions, reductions, and relative dose intensity will also be summarized.

9.7 Efficacy Analyses

9.7.1 Overall Response Rate

The ORR by RECIST v 1.1 will be defined as the proportion of patients with a best overall response (BOR) of CR or PR. The overall response category will be derived based on response assessment performed on or before the start of subsequent anti-cancer therapy.

The percentage of ORR with its 95% confidence interval (CI) will be presented. In contrast to CR, PR, or PD, a BOR of SD can only be made after the patient is on-study for a minimum of 35 days after the first dose of study drug. Any tumor assessment indicating SD before this time period will be considered as a non-evaluable for BOR if no assessment after this time period is available.

9.7.2 Duration of Response

Duration of response by RECIST 1.1 will be defined among responders (CR or PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause.

The date of disease progression will be defined as the earliest date of disease progression. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method for all responders and by response (CR/PR). The median duration of response and 95% CI will be presented. Further details will be outlined in the SAP.

9.7.3 Progression-Free Survival

PFS will be defined as the time from first dose of study drug until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression. For patients whose disease has not progressed at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method. The median PFS time and 95% CI will be presented. Further details will be outlined in the SAP.

9.7.4 Overall Survival

Median OS will be defined as the time from the first dose of study drug until death due to any cause. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. The data will be analyzed by the Kaplan-Meier method. The median OS and 95% CI will be presented. Further details will be outlined in the SAP.

9.8 Safety Analyses

Safety analyses will be presented descriptively.

9.8.1 Adverse Events

The focus of AE summarization will be on TEAEs. A TEAE is defined as an AE that occurs or worsens in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study or start of a new anticancer therapy, whichever is earlier.

All TEAEs will be summarized. Summary tables will be presented to show the number of patients reporting TEAEs by severity grade and corresponding percentages. A patient who reports multiple TEAEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade.

Separate summaries will be prepared for TEAEs classified as severe or life-threatening (≥Grade 3); study drug-related AEs; AEs leading to treatment interruption, modification, or discontinuation; AESIs; SAEs; and death.

9.8.2 Clinical Laboratory Results

Clinical hematology, coagulation panel, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Shifts for clinical laboratory results that can be graded according to CTCAE version 4.0 will be summarized by CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in "worst-case post-Baseline" summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. Further details will be provided in the SAP.

9.8.3 Additional Safety Assessments

The results of scheduled assessments of vital signs, physical examinations, ECOG performance status, and 12-lead ECGs will be summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in "worst case" summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. All data will be listed. Further details will be provided in the SAP.

9.9 Pharmacokinetic Analyses

The PK profile will include determination of: maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), area under the concentration-time curve from time zero to the end of the dosing interval (AUC_{tau}), area under the concentration-time curve from time zero to infinity (AUC_{inf}), apparent terminal elimination half-life (T_{half}), CL, volume of distribution (V_d), and accumulation index (AI).

Pharmacokinetic parameters will be determined for all PK-evaluable patients using a non-compartmental method with Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ, US) or other appropriate software. Results will be reported as part of the CSR. Supplemental analysis may be performed, as appropriate, by integrating with data from other camidanlumab tesirine studies, and would be reported separately.

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9.10 Immunogenicity Analyses

A tiered immunogenicity strategy (Figure 3) will be undertaken to evaluate ADAs by screening and confirmatory assays with titer evaluation, followed by characterization and evaluation of neutralizing capacity as needed. ADA sample collection, banking, and testing in validated and to be validated assays will be according to the new FDA Draft Guidance for Industry (April 2016): 'Assay Development and Validation for Immunogenicity testing of Therapeutic Protein Products'

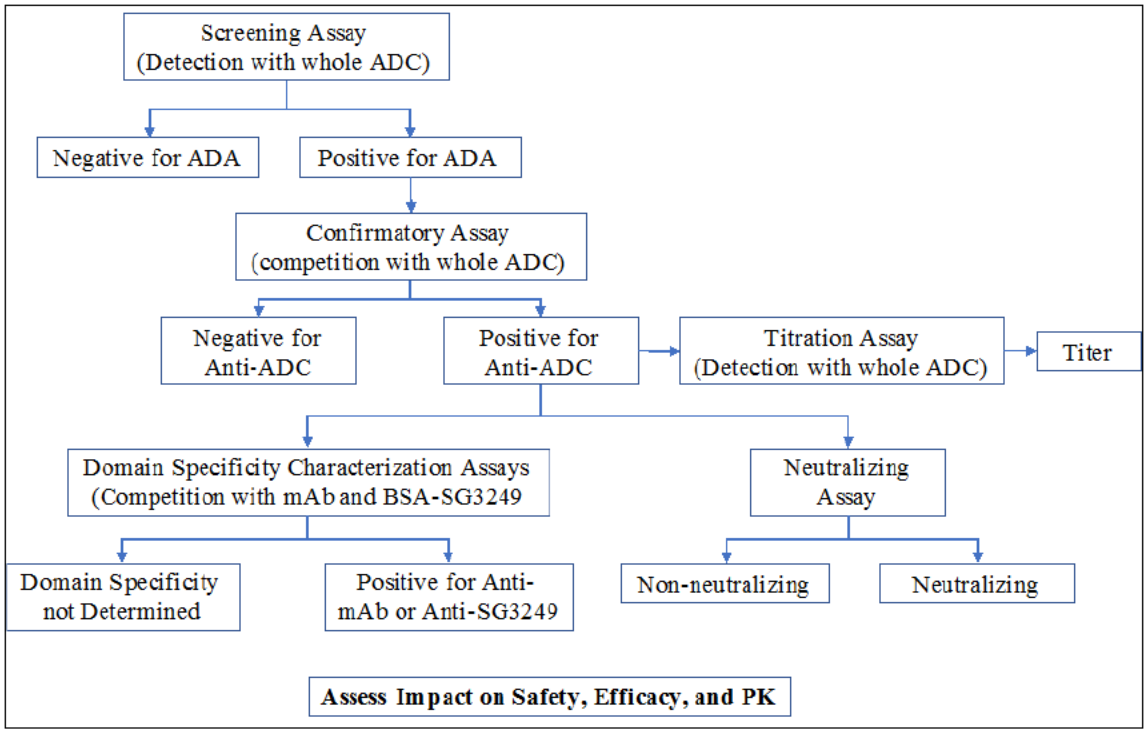

Figure 3. Anti-drug Antibody Tiered Immunogenicity Testing Strategy

Abbreviations: ADA=anti-drug antibody; ADC=antibody-drug conjugate; BSA=bovine serum albumin; mAb=monoclonal antibody; PK=pharmacokinetics.

Results from ADA testing will include tabular summarization for number/proportion of patients with positive pre-dose ADA response, number of patients with post-dose ADA response only, and number of patients with positive ADA response at any time. The denominator will be the total number of patients tested for ADAs in the study. For patients exhibiting a positive ADA, PK, safety and efficacy correlates will be assessed and reported.

[redacted]

10 DATA MANAGEMENT AND QUALITY ASSURANCE

The Investigator will maintain accurate source documentation including patient medical records, laboratory reports, ECG strips, and patient diaries.

Investigative site qualified personnel will enter patient data into an EDC system. The analysis data sets will be a combination of these data and data from other sources.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the world health organization (WHO) Drug Dictionary.

After database lock, each study site will receive information about all of their site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a copy of study data from all sites will be created and sent to the Sponsor for storage. The CRO will maintain a duplicate copy for its records. In all cases, patient initials will not be collected or transmitted to the Sponsor.

For detailed instruction on data entry procedures and timelines, please refer to the eCRF Completion Guidelines.

11 ETHICAL, REGULATORY, AND STUDY MANAGEMENT CONSIDERATIONS

11.1 Regulatory and Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and all applicable regulations.

11.2 Independent Ethics Committee or Institutional Review Board

Federal regulations and ICH guidelines require that approval be obtained from an institutional review board (IRB)/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study intended to be provided to the patient or the patient's legally authorized representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for obtaining continued review of the clinical research as specified by the IRB/IEC, at intervals not exceeding 1 year. The Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

11.3 Patient Information and Consent

Informed consent in compliance with IRB/IEC and local regulations shall be obtained from each patient or their legally authorized representative before performing any study procedures and will be documented with a signed IRB/IEC approved ICF. Before enrollment, each prospective patient or his or her legally authorized representative will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legally authorized representative understands the implications of participating in the study, the patient/legally authorized representative will be asked to give consent to participate in the study and sign the ICF. The process for obtaining consent has to be documented at the institution.

If the ICF is revised during the course of the study, all patients on-study, including those in follow-up, must sign the revised form, unless otherwise indicated by the IRB/IEC (local or global, as applicable). In such cases, the reason for not re-consenting the patient should be documented.

11.4 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, regulatory authorities, or the IRB/IEC.

The Investigator and other study staff may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements as required under 21 CFR 54 and local regulations. In addition, the Investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

11.6 Study Conduct

The Investigator will conduct all aspects of this study in accordance with the principles of the current version of ICH E6 as well as all national, state, and local laws and regulations. Study personnel involved in conducting this study will be qualified by education training and experience to perform their respective tasks. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

11.7 Protocol Amendments

Any change in the study plan requires a protocol amendment. All amendments to the protocol must be reviewed and approved following the same process as the original protocol before the amended protocol can be implemented. The Investigator will inform the governing IRB/IEC of all protocol amendments issued by the Sponsor in accordance with established IRB/IEC procedure. Only protocol amendments intended to eliminate an apparent immediate hazard to patient(s) may be implemented immediately, i.e., without IRB/IEC approval, but the circumstances of the change must be documented and submitted to the IRB/IEC.

11.8 Monitoring of the Study

All aspects of the study will be carefully monitored by the Sponsor or designee for compliance with GCP and applicable government regulations.

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency access to all study records.

The Investigator should promptly notify the Sponsor and the CRO of any inspections scheduled by any regulatory authorities and promptly forward copies of any inspection reports received to the Sponsor.

11.9 Records Retention

Essential documents should be retained for at least 15 years from the completion of the study (last patient last visit) or until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational study drug. However, these documents should be retained

for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

11.10 Publications

Following completion of the study, the results from the study may be reported publicly by making any oral public presentation and/or submitting or presenting a manuscript, abstract, or other materials relating to the Study at scientific meetings and/or to a publisher, reviewer, or other outside person in scientific journals ("Publication"), provided, however, that Publication of the results from an individual site shall not be made before the first multi-site Publication by Sponsor. The Sponsor shall coordinate the drafting, editing, authorship, and other activities related to study Publication and shall mutually agree with the Investigator(s) on the number, medium, forum, and timing for Publication. The Sponsor shall solicit input regarding contents of the Publication from all Investigators and in consultation with all sites. The Sponsor acknowledges the right of the Investigator(s) to publish the results of this study after the entire study has completed, but also reserves the right to a window to review the Publication for regulatory compliance as well as for protection of its intellectual property. In particular, the Sponsor may request to remove the Sponsor's confidential information and suspend Publication for a certain period of time to protect the Sponsor's intellectual property interest, as further set forth in the Clinical Trial Agreement with the clinical study site(s) and Investigator(s).

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