NCT #: NCT04590781

CLINICAL STUDY PROTOCOL

A Phase 1b/2 Multiple-Dose Study to Evaluate the Safety and Efficacy of XmAb®18087 ± Pembrolizumab in Subjects with Advanced Merkel Cell Carcinoma or Extensive-stage Small Cell Lung Cancer (DUET-1-02)

Protocol No.:	XmAb18087-02
IND No.:	IND 136250
Test Product:	XmAb®18087
Indications:	Advanced Merkel Cell Carcinoma, Extensive-Stage Small Cell Lung Cancer
Sponsor:	Xencor, Inc. 111 West Lemon Avenue Monrovia, CA 91016
Development Phase:	Phase 1b/2
Sponsor Medical Expert:	[redacted] [redacted] Telephone: [redacted] Email: [redacted]
Version and Date:	Version 1.0 (18 August 2020)

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator, potential Investigator or consultant for review by you, your staff and applicable Independent Ethics Committee and/or Institutional Review Board. It is understood that the information will not be disclosed to others without written authorization from Xencor, Inc. except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SIGNATURE PAGES

Declaration of Sponsor or Responsible Medical Expert

PROTOCOL TITLE: A Phase 1b/2 Multiple-Dose Study to Evaluate the Safety and Efficacy of XmAb®18087 ± Pembrolizumab in Subjects with Advanced Merkel Cell Carcinoma or Extensive-stage Small Cell Lung Cancer (DUET-1-02)

PROTOCOL NUMBER: XmAb18087-02

Xencor, Inc.

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2013), and the current guidelines on good clinical practices (GCP) applicable to this clinical study.

{See appended electronic signature page at the end of the document}

[redacted]
Xencor, Inc.

SIGNATURE PAGE

Declaration of the Principal Investigator

PROTOCOL TITLE: A Phase 1b/2 Multiple-Dose Study to Evaluate the Safety and Efficacy of XmAb®18087 ± Pembrolizumab in Subjects with Advanced Merkel Cell Carcinoma or Extensive-stage Small Cell Lung Cancer (DUET-1-02)

This clinical study protocol was subjected to critical review and has been released by the Sponsor. I have read this protocol and agree that the information it contains is consistent with current risk and benefit evaluation of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2013), and the current guidelines on GCP applicable to this clinical study.

I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I will perform the study according to specifications outlined in the protocol and agree to implement protocol requirements only after this protocol version and the subject information/informed consent forms (ICF) have been approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC). I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB/IEC. I will submit any protocol modifications (amendments) and/or any ICF modifications to the Sponsor and the IRB/IEC, and approval will be obtained before any modifications are implemented.

I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor, Xencor, Inc., unless this requirement is superseded by a regulatory authority, eg, United States (US) Food and Drug Administration (FDA).

I agree to conduct the study as outlined in this clinical study protocol dated 18 August 2020. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Investigator(s) and must be documented in writing.

Principal Investigator

Name, Title	Date (Day/Month/2020)

GENERAL INFORMATION

Protocol Title:	A Phase 1b/2 Multiple-Dose Study to Evaluate the Safety and Efficacy of XmAb®18087 ± Pembrolizumab in Subjects with Advanced Merkel Cell Carcinoma or Extensive-stage Small Cell Lung Cancer (DUET-1-02)
Protocol No.:	XmAb18087-02
Protocol Date:	Version 1.0, Original (18 August 2020)
Sponsor:	Xencor, Inc 111 West Lemon Avenue Monrovia, CA 91016
Sponsor Medical Monitor:	[redacted] [redacted] Telephone: [redacted] Email: [redacted]
Adverse Event Reporting:	ICON Clinical Research Emergency phone number: [redacted] (Toll free for US) [redacted] (Toll number for US and outside of US) E-mail: [redacted] (Americas) [redacted] (Europe)
Clinical Research Organization:	ICON Clinical Research Ltd South County Business Park Leopardstown Ireland
Clinical Laboratories:	ICON Laboratory Services 123 Smith Street Farmingdale, NY 11735
Bioanalytical Laboratory (PK):	See Laboratory Manual for contact information.
Cytokine Laboratory:	See Laboratory Manual for contact information.
Immunogenicity (ADA) Assessment Laboratory:	See Laboratory Manual for contact information.
Flow Cytometry, B Cell, NK Cell T Cell Assessment, and Immunohistochemistry Laboratory	See Laboratory Manual for contact information.
Merkel cell polyoma virus antibody assay and Immunohistochemistry Laboratory	See Laboratory Manual for contact information.

2. SYNOPSIS

Name of Sponsor/Company: Xencor, Inc.		
Name of Investigational Product: XmAb®18087		
Name of Active Ingredient: XmAb18087		
Protocol Number: XmAb18087-02	**Phase:** 1b/2	**Country:** United States
Title of Study: A Phase 1b/2 Multiple-Dose Study to Evaluate the Safety and Efficacy of XmAb®18087 ± Pembrolizumab in Subjects with Advanced Merkel Cell Carcinoma or Extensive-stage Small Cell Lung Cancer (DUET-1-02)		
Study Center(s): It is planned that up to 25 study centers will be initiated for this study in the United States.		
Publications: None		
Planned Study Period: Estimated date first subject enrolled: 31 March 2021 Estimated date last subject completed: 30 June 2024	**Development Phase:** Phase 1b/2	

Objectives:

Primary Objectives:

The primary objectives of the study are as follows:

1. To determine the safety and efficacy (by overall response rate [ORR], complete response [CR], and partial response [PR] per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria) of XmAb18087 monotherapy in subjects with advanced Merkel cell carcinoma (MCC) that has progressed after treatment with standard therapies
2. To determine the safety and efficacy (by ORR, CR, and PR per RECIST 1.1 criteria) of XmAb18087 in combination with pembrolizumab in subjects with advanced MCC who have not received prior anti-programmed cell death 1 (PD1) or anti-programmed cell death ligand 1 (PDL1) therapies, and for whom pembrolizumab as a single agent is indicated
3. To determine the safety and efficacy (by ORR, CR, and PR per RECIST 1.1 criteria) of XmAb18087 monotherapy in subjects with extensive-stage small cell lung cancer (SCLC) that has progressed after treatment with standard therapies

Secondary Objectives:

The secondary objectives of the study are as follows:

1. To assess antitumor activity of XmAb18087 by progression-free survival (PFS) per RECIST 1.1 criteria, as well as overall survival (OS) and duration of response, when administered with and without pembrolizumab in subjects with advanced MCC, and as monotherapy in subjects with extensive-stage SCLC
2. To characterize the pharmacokinetics (PK) and immunogenicity of XmAb18087 administered with and without pembrolizumab in subjects with advanced MCC, and as monotherapy in subjects with extensive-stage SCLC
3. To assess the PK profile (maximum observed serum concentration [C_{max}] and $C_{min[trough]}$) of pembrolizumab when co-administered with XmAb18087

Exploratory Objectives:

The exploratory objectives of the study are as follows:

1. To assess the incidence, timing, and severity of cytokine release syndrome (CRS) by the following:
   a. CRS-related adverse events (AEs), incidence and grade of AEs and incidence of serious adverse events [SAEs])
   b. Biomarkers of CRS
2. To characterize the response to administration of XmAb18087 with and without pembrolizumab by assessment of cell surface markers on selected immune system cells in peripheral blood, including changes in lymphocyte subsets and in T-cell activation/exhaustion by flow cytometry and similar bioanalytical methods
3. To characterize pharmacodynamics (PD) by correlation of response with NETSPOT® (gallium 68 dotatate) positron emission tomography/computed tomography (PET/CT) scan results after XmAb18087 administration with and without pembrolizumab
4. To evaluate by immunohistochemistry tumor-cell expression of somatostatin receptor 2 (SSTR2) and PDL1 on tumor cells and tumor-infiltrating T cells for expression of proliferation markers and PD1/PDL1 after XmAb18087 administration with and without pembrolizumab, as well as changes in other immune cell subsets
5. To characterize the pharmacodynamic changes in the intratumoral inflammatory response using immunostaining of immune cells and analysis of RNA signatures
6. To correlate response in MCC subjects to Merkel cell polyomavirus (MCPyV) status as determined by serology and immunohistochemistry

Methodology:

This is a Phase 1b/2, multiple-dose study designed to describe safety and efficacy, and to assess PK and immunogenicity of XmAb18087 monotherapy and in combination with pembrolizumab in subjects with metastatic MCC or locoregional MCC that has recurred after locoregional therapy with surgery and/or radiation therapy, and XmAb18087 monotherapy in subjects with extensive-stage SCLC that has progressed after standard therapies.

Part A of the study will enroll safety run-in cohorts of subjects with advanced MCC that has progressed after treatment with standard therapies to confirm the safety and tolerability of the XmAb18087 monotherapy administered intravenously (IV) with weekly step-up dosing for 42-day cycles. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 monotherapy using the recommended dose (RD) identified following the safety run-in.

Part B of the study will enroll safety run-in cohorts of subjects with advanced MCC not previously treated with anti-PD1 or anti-PDL1 agents, and for whom pembrolizumab as a single agent is indicated, to confirm the safety and tolerability of XmAb18087 in combination with pembrolizumab. Subjects will receive step-up IV dosing of XmAb18087 on Days 1, 8, 22, 29, and 36, and IV dosing of pembrolizumab on Day 15 of each 42-day cycle. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 plus pembrolizumab combination therapy using the RD identified following the safety run-in.

Enrollment into the first safety run-in cohort of Part B (Cohort 1B) may begin after the first safety run-in cohort in Part A (Cohort 1A, one dose level higher than Cohort 1B) has completed the first cycle and the regimen has been demonstrated to be tolerable.

Part C of the study will enroll safety run-in cohorts of subjects with extensive-stage SCLC that has progressed after treatment with standard therapies to confirm the safety and tolerability the same XmAb18087 monotherapy. The safety run-in will follow the same cohort schema as described for Part A to identify a RD for expansion in SCLC. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 monotherapy using the RD identified following the safety run-in.

Enrollment into Part C may begin concurrently with Part A.

Termination of Study

If the Investigator or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects should the clinical study continue, the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study also may be terminated at the Sponsor's discretion, also in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study.

- Failure to enroll subjects at the required rate.
- A decision of the Sponsor to suspend or discontinue development of the investigational medicinal product (IMP).

Should the study be terminated and/or the site closed for whatever reason, all documentation pertaining to the study and IMP must be returned to the Sponsor. Any actions required for assessing or maintaining subject safety will continue as required, despite termination of the study by the Sponsor.

Treatment Plan:

Part A, which will enroll subjects with previously treated advanced MCC, consists of safety-run in cohorts followed by an expansion cohort. For the first safety run-in cohort (Cohort 1A), 3 to 6 subjects will be enrolled and will receive step-up dosing as follows: 0.3 µg/kg on Day 1, followed by 1.0 µg/kg on Days 8, 15, 22, 29, and 36 of the first cycle, and Days 1, 8, 15, 22, 29, and 36 of all subsequent cycles. If the Cohort 1A regimen is not tolerated, lower dose levels may be explored. If the Cohort 1A regimen is tolerated, 3 to 6 subjects will be enrolled in Cohort 2A and will receive step-up dosing as follows: 0.3 µg/kg on Day 1, 1.0 µg/kg on Day 8, and 2.0 µg/kg on Days 15, 22, 29, and 36 of the first cycle and Days 1, 8, 15, 22, 29, and 36 of all subsequent cycles. If this regimen is tolerated, 3 to 6 subjects will be enrolled in Cohort 3A and will receive step-up dosing as follows: 0.3 µg/kg on Day 1, 1.0 µg/kg on Day 8, 2.0 µg/kg on Day 15, and 4.0 µg/kg on Days 22, 29, and 36 of the first cycle and Days 1, 8, 15, 22, 29, and 36 of all subsequent cycles. See Cohort Table A.

Based on assessments of tolerability, safety, and PK data from all the safety run-in cohorts in Part A, an RD regimen for expansion will be selected. Up to 9 subjects will be enrolled at the RD. If at least 1 subject shows a response by RECIST 1.1 criteria, then enrollment will continue up to a total of 22 subjects to evaluate efficacy.

Part B, which will enroll subjects with advanced MCC not previously treated with anti-PD1 or anti-PDL1 agents, consists of safety run-in cohorts followed by an expansion cohort. Safety run-in Cohort 1B (one dose level below Cohort 1A) will begin enrolling after Cohort 1A is completed and the dosing regimen is deemed tolerable. For all Part B cohorts, 400 mg pembrolizumab will be administered IV on Day 15 of each 42-day cycle. Three to 6 subjects will be enrolled in Cohort 1B and will receive XmAb18087 administered IV as follows: 0.3 µg/kg on Days 1, 8, 22, 29, and 36 of all cycles. If this regimen is tolerated, 3 to 6 additional safety run-in subjects will be enrolled in Cohort 2B and will receive step-up IV dosing of XmAb18087 as follows: 0.3 µg/kg on Day 1, then 1.0 µg/kg on Days 8, 22, 29, and 36 of the first cycle and Days 1, 8, 22, 29, and 36 of all subsequent cycles. If this regimen is tolerated, 3 to 6 subjects will be enrolled in Cohort 3B and will receive step-up IV dosing of XmAb18087 as follows: 0.3 µg/kg on Day 1, 1.0 µg/kg on Days 8 and 22, then 2.0 µg/kg on Days 29 and 36 of the first cycle and Days 1, 8, 22, 29, and 36 of all subsequent cycles. If this regimen is tolerated, 3 to 6 subjects will be enrolled in Cohort 4B and will receive step-up IV dosing of XmAb18087 as follows: 0.3 µg/kg on Day 1, 1.0 µg/kg on Days 8 and 22, 2.0 µg/kg on Days 29 and 36 of the first cycle and Day 1 of all subsequent cycles, and 4.0 µg/kg and Days 1, 8, 22, 29, and 36 of all cycles after the first cycle. See Cohort Table B.

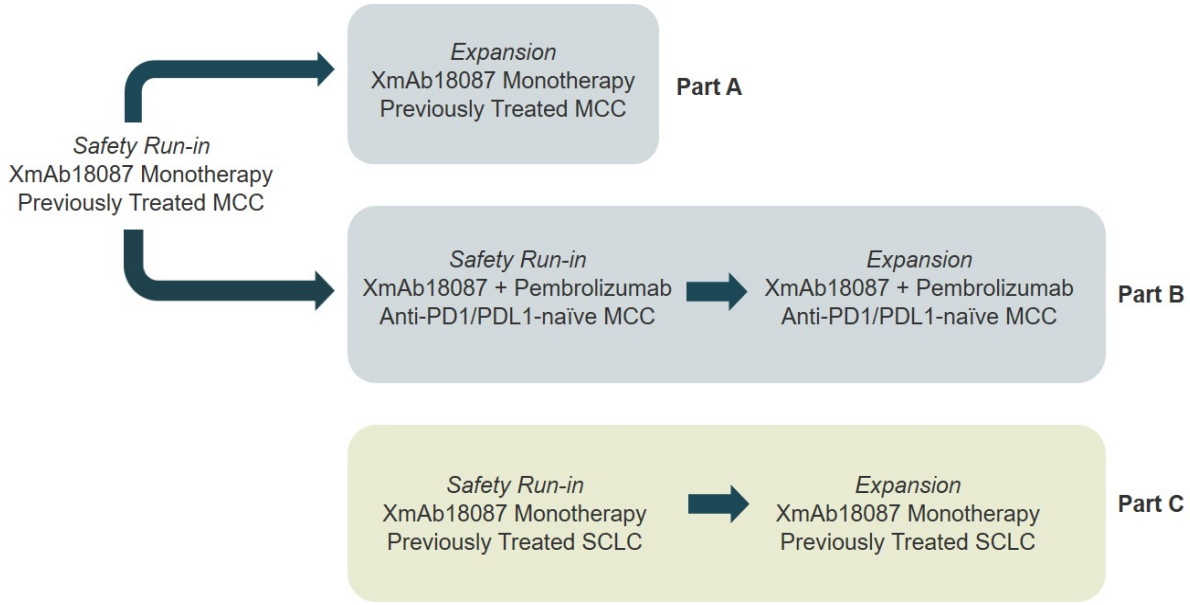
Based on assessments of tolerability, safety, and PK data from all the safety run-in cohorts in Part B, an RD for expansion will be selected. Up to 12 subjects will be enrolled at the RD. If at least 4 subjects show a response by RECIST 1.1 criteria, enrollment will continue up to a total of 30 subjects to evaluate efficacy.

Part C will enroll subjects with previously treated extensive-stage SCLC and consists of safety-run in cohorts followed by an expansion cohort. Part C will follow the same safety run-in schema as described for Part A. See Cohort Table C.

Based on assessments of tolerability, safety, and PK data from all the safety run-in cohorts in Part C, an RD for expansion will be selected. Up to 9 subjects will be enrolled at the RD. If at least 1 subject shows a response by RECIST 1.1 criteria, then enrollment will continue up to a total of 30 subjects to evaluate efficacy. Throughout the study, SSTR2 expression levels and prevalence will be assessed histologically using tumor biopsies from enrolled subjects; a higher number of subjects may be enrolled in the Part C expansion cohort based on these assessments.

Parts A, B, and C: The decision to advance to higher dose levels after each safety run-in cohort will be made by a Safety Review Committee (SRC) based on review of the aggregate safety data for all subjects in that cohort as well as cumulative safety data for the study overall. The SRC will be allowed to make adaptations to the dosing schema, if needed, in accordance with evolving trial safety and tolerability findings, as long as adaptations do not significantly increase subject risk. Any such adaptations would require a protocol amendment and Institutional Review Board (IRB) approval.

Schema:



MCC = Merkel cell carcinoma; PD1 = programmed cell death protein 1; PDL1 = programmed cell death ligand 1; SCLC = small cell lung cancer.

Number of Subjects:

Up to 142 subjects will be enrolled.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria for All Cohorts

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

- Able to provide written informed consent
- Adult subjects ≥ 18 years
- Disease measurable by RECIST 1.1 criteria using either CT or magnetic resonance imaging (MRI) scan
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- All subjects must have adequate archival tumor sample (slides or archival formalin-fixed paraffin-embedded [FFPE] block[s] containing tumor that has not been previously irradiated; FFPE blocks are preferred to slides, and newly obtained biopsies are preferred to archived tissue. Refer to the laboratory manual for further instructions). Excepted are subjects who consent to having a fresh tumor biopsy to provide a fresh tumor sample instead of the archival tumor sample.
- Female subjects of childbearing potential must agree to use a highly effective method of birth control during and for 4 weeks after completion of study. Women are considered to be of childbearing potential unless it is documented that they are over the age of 60 OR postmenopausal by history with no menses for 1 year and confirmed by follicle-stimulating hormone (FSH; using local reference ranges) OR have a history of hysterectomy and/or bilateral oophorectomy OR have a history of bilateral tubal ligation. Highly effective methods of birth control include combined hormonal birth control (oral, intravaginal, or transdermal), or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or intrauterine), intrauterine devices (IUDs), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (provided partner is the sole sexual partner and there has been a medical assessment of surgical success), or sexual abstinence as defined in Section 8.9.1.
- Fertile male subjects must be willing to practice a highly effective method of birth control for the duration of the study and continuing for 4 weeks after the last dose of XmAb18087 or pembrolizumab (when applicable).

Highly effective methods of birth control include vasectomy or a condom in combination with double-barrier methods, spermicide, hormonal birth control, or IUD (nonhormonal) used by the woman.

- Able and willing to complete the entire study according to the study schedule

Additional Inclusion Criteria for Part A and Part B Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Parts A and B safety run-in and expansion cohorts:

- Histologically or cytologically confirmed metastatic MCC or locoregional MCC that has recurred following standard locoregional therapy with surgery and/or radiation therapy

Additional Inclusion Criteria for Part A Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Part A safety run-in and expansion cohorts:

- Subjects must have progressed on or been ineligible for treatment with anti-PD1 or anti PDL1 therapy.

Additional Inclusion Criteria for Part B Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Part B safety run in and expansion cohorts:

- Subjects must be eligible to receive pembrolizumab as standard of care.

Additional Inclusion Criteria for Part C Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Part C safety run-in and expansion cohorts:

- Histologically or cytologically confirmed extensive-stage SCLC that has progressed following standard therapies

Exclusion Criteria for All Cohorts

Subjects who meet any of the following criteria will be excluded from the study:

- History of prior organ or bone marrow transplant
- History of chronic lymphocytic leukemia
- Subjects currently receiving anticancer therapies
- Subjects who have received anticancer therapies within 2 weeks of the start of study drug (including chemotherapy, radiation therapy, immunotherapy, etc.)
- Prior therapy with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA4, OX40, CD137) AND were permanently discontinued from that treatment due to an immune-related adverse event (IRAE)
- Failure to recover from any IRAE from prior cancer therapy to ≤ Grade 1 (participants with ≤ Grade 2 neuropathy or endocrinopathies controlled by hormone replacement are eligible)
- Failure to recover from any other toxicity (other than immune-related toxicity) from previous anticancer treatment to ≤ Grade 2
- Known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 28 days prior to trial treatment.
- Have a history of (noninfectious) pneumonitis that required steroids or have current pneumonitis (history of radiographically visible but asymptomatic radiation pneumonitis is allowed)
- Platelet count $< 50 \times 10^9$/L
- Absolute neutrophil count $< 1.0 \times 10^9$/L
- Aspartate aminotransferase (AST) ≥ 3 × upper limit of normal (ULN), or if subject has known liver metastases, AST ≥ 7 × ULN
- Alanine aminotransferase (ALT) ≥ 3 × ULN, or if subject has known liver metastases, ALT ≥ 7 × ULN

- Estimated creatinine clearance < 50 mL/min calculated by the Cockcroft Gault or Modification of Diet in Renal Disease formulas at screening
- Treatment with immunosuppressive therapy within 28 days of first dose of study drug
- History or evidence of any other clinically unstable/uncontrolled disorder, condition, or disease (including, but not limited to, cardiopulmonary, renal, metabolic, hematologic, or psychiatric) other than their primary malignancy that in the opinion of the Investigator would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
- Treatment for any serious bacterial, viral, parasitic, or systemic fungal infections within the 30 days prior to study entry
- Active known or suspected COVID-19 disease
- Active known or suspected autoimmune disease (except that subjects are permitted to enroll if they have vitiligo; type 1 diabetes mellitus; residual hypothyroidism due to an autoimmune condition that is treatable with hormone replacement therapy only; psoriasis, atopic dermatitis, or another autoimmune skin condition that is managed without systemic therapy; or arthritis that is managed without systemic therapy beyond oral acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDS])
- Positive test for human immunodeficiency virus (HIV) or hepatitis C antibodies
- Positive test for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb; a subject whose HBsAg is negative and HBcAb is positive may be enrolled if a hepatitis B virus [HBV] DNA test is negative and either the subject is treated with potent antiviral therapy or is retested for HBsAg and HBV DNA every month)
- Subject is pregnant or breastfeeding, planning to become pregnant, or expecting to conceive or father children while enrolled in the study, up to the end of study (EOS) visit.
- Positive serum pregnancy test (ie, urine human chorionic gonadotropin) at screening

Additional Exclusion Criteria for Part B Cohorts:

In addition to the exclusion criteria above, subjects will be excluded from Part B cohorts administered XmAb18087 in combination with pembrolizumab if they meet the following criteria:

- Prior treatment with therapeutics directed at anti-programmed cell death 1 (anti-PD1) or anti-programmed cell death ligand 1 (anti-PDL1)
- Have severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients

Test Product, Dose, and Mode of Administration:

XmAb18087 is a humanized bispecific antibody (bsAb) that binds both the tumor antigen SSTR2 and CD3 antigen to recruit cytotoxic T cells for killing of $SSTR2^{+}$ tumor cells. [redacted]

The cohorts and dose levels to be administered in this clinical trial are shown below.

Cohorts

Cohort Table A: Part A (MCC) Monotherapy Safety Run-in and Expansion Cohorts

	Cycle and Day	Cycle 1							Cycle 2+							Subjects
		D1	D8	D15	D22	D29	D36	D40 ± 2	D1	D8	D15	D22	D29	D36	D40 ± 2	
	Drug	XmAb18087 (µg/kg)						EA	XmAb18087 (µg/kg)						EA	
	Study Day	1	8	15	22	29	36	40	43	50	57	64	71	78	82	
Part A (Safety Run-in)	1A	0.3	**1.0**	1.0	1.0	1.0	1.0	---	1.0	1.0	1.0	1.0	1.0	1.0	---	3 – 6
	2A	0.3	1.0	**2.0**	2.0	2.0	2.0	---	2.0	2.0	2.0	2.0	2.0	2.0	---	3 - 6
	3A	0.3	1.0	2.0	**4.0**	4.0	4.0	---	4.0	4.0	4.0	4.0	4.0	4.0	---	3 - 6
Part A (Expansion)	Expansion A	At RD cohort														Up to 22

D = day; EA = efficacy assessment (no drug administered). Maximum escalated dose for each cohort in bold.

Cohort Table B: Part B (MCC) Combination Therapy Safety Run-in and Expansion Cohorts

	Cycle and Day	**Cycle 1**							**Cycle 2+**							**Subjects**
		D1	**D8**	**D15**	**D22**	**D29**	**D36**	**D40 ± 2**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D40 ± 2**	
	Drug	**XmAb18087 (µg/kg)**		**Pem (mg)**	**XmAb18087 (µg/kg)**			**EA**	**XmAb18087 (µg/kg)**		**Pem (mg)**	**XmAb18087 (µg/kg)**			**EA**	
	Study Day	**1**	**8**	**15**	**22**	**29**	**36**	**40**	**43**	**50**	**57**	**64**	**71**	**78**	**82**	
Part B (Safety Run-in)	1B	**0.3**	0.3	400	0.3	0.3	0.3	---	0.3	0.3	400	0.3	0.3	0.3	---	3 – 6
	2B	0.3	**1.0**	400	1.0	1.0	1.0	---	1.0	1.0	400	1.0	1.0	1.0	---	3 – 6
	3B	0.3	1.0	400	1.0	**2.0**	2.0	---	2.0	2.0	400	2.0	2.0	2.0	---	3 – 6
	4B	0.3	1.0	400	1.0	2.0	2.0	---	2.0	**4.0**	400	4.0	4.0	4.0	---	3 – 6
Part B (Expansion)	Expansion B	At RD cohort														Up to 30

D = day; EA = efficacy assessment (no drug administered); Pem = pembrolizumab. Maximum escalated dose for each cohort in bold.

Cohort Table C: Part C (SCLC) Monotherapy Safety Run-in and Expansion Cohorts

	Cycle and Day	Cycle 1							Cycle 2+							Subjects
		D1	D8	D15	D22	D29	D36	D40 ± 2	D1	D8	D15	D22	D29	D36	D40 ± 2	
	Drug	XmAb18087 (µg/kg)						EA	XmAb18087 (µg/kg)						EA	
	Study Day	1	8	15	22	29	36	40	43	50	57	64	71	78	82	
Part C (Safety Run-in)	1C	0.3	**1.0**	1.0	1.0	1.0	1.0	---	1.0	1.0	1.0	1.0	1.0	1.0	---	3 - 6
	2C	0.3	1.0	**2.0**	2.0	2.0	2.0	---	2.0	2.0	2.0	2.0	2.0	2.0	---	3 – 6
	3C	0.3	1.0	2.0	**4.0**	4.0	4.0	---	4.0	4.0	4.0	4.0	4.0	4.0	---	3 - 6
Part C (Expansion)	Expansion C	At RD cohort														Up to 30

D = day; EA = efficacy assessment (no drug administered). Maximum escalated dose for each cohort in bold.

Reference Therapy, Dosage, and Mode of Administration:

None

Duration of Treatment:

Each treatment cycle (Parts A, B, and C) is 42 days long. In Parts A and C, each cycle will consist of 6 weekly doses of XmAb18087 (on Days 1, 8, 15, 22, 29, and 36). In Part B, each cycle will consist of 6 weekly doses of either XmAb18087 or pembrolizumab: 5 doses of XmAb18087 (on Days 1, 8, 22, 29, and 36) and 1 dose of pembrolizumab (on Day 15).

Criteria for Evaluation:

Safety:

As assessed by AEs, vital signs, physical examination (PE) findings, clinical laboratory safety assessments, and electrocardiogram (ECG) parameters:

- Incidence of treatment-emergent AEs (TEAEs), treatment-emergent serious adverse events (TESAEs), treatment-related TEAEs and TESAEs, TEAEs by severity as defined in the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and TEAEs resulting in the permanent discontinuation of XmAb18087 or pembrolizumab.

Efficacy:

Antitumor activity of XmAb18087 as assessed by response rates (ORR, CR rate, PR rate), duration of response, PFS, and OS.

Pharmacokinetics:

Pharmacokinetic parameters including C_{max}, time to reach maximum concentration (t_{max}), half-life ($t_{1/2}$), area under the serum concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), clearance (CL), volume of distribution (Vd), and volume of distribution at steady state (Vd_{ss}) will be estimated using either noncompartmental or compartmental methods, whichever best describes the observed data. Pharmacokinetic parameters for XmAb18087 will be compared with and without pembrolizumab administration.

Pharmacodynamics:

Baseline and serial assessment of B-cell, NK-cell, and T-cell numbers and T-cell activation will be assessed in peripheral venous blood.

Endpoints:

Primary Endpoints:

The primary endpoints are as follows:

- Safety of (1) XmAb18087 monotherapy in MCC and SCLC, and (2) XmAb18087 and pembrolizumab combination therapy in MCC, as assessed by the following:
  - Incidence of TEAEs
  - Incidence of clinically significant changes in safety laboratory tests, PE findings, vital signs, and ECGs
  - Incidence and severity of CRS
- Efficacy of (1) XmAb18087 monotherapy in MCC and SCLC, and (2) XmAb18087 and pembrolizumab combination therapy in MCC using RECIST 1.1 assessment of CT/MRI imaging, as well as aggregate data, for the following:
  - ORR
  - CR rate
  - PR rate

Secondary Endpoints:

The secondary endpoints are as follows:

- Efficacy of (1) XmAb18087 monotherapy in MCC and SCLC, and (2) XmAb18087 and pembrolizumab combination therapy in MCC using RECIST 1.1 assessment of CT/MRI imaging, as well as aggregate data, for the following:
  - Duration of response

- PFS
- OS

- PK characterization of XmAb18087, when administered as monotherapy and in combination with pembrolizumab, based on the parameters of C_{max}, t_{max}, $t_{1/2}$, $AUC_{0-\infty}$, CL, Vd, and Vd_{ss}. Further details will be defined in a PK analysis plan.
- Assessment of immunogenicity by incidence of anti-XmAb18087 antibodies and qualitative assessment of safety outcomes
- PK characterization of pembrolizumab, when administered in combination with XmAb18087, based on parameters similar to those for XmAb18087, with further details to be provided in a PK analysis plan.

Exploratory Endpoints:

The exploratory endpoints are as follows:

- Assessment of peripheral blood for cell surface markers by flow cytometry and similar bioanalytical methods that evaluate the response of selected immune system cells following administration of XmAb18087 as a monotherapy and in combination with pembrolizumab, including changes in lymphocyte subsets and in T-cell activation and exhaustion markers
- PD characterized by NETSPOT (gallium 68 dotatate) PET/CT results and by tumor cell expression of SSTR2 and PDL1 and tumor-infiltrating immune-cell expression of PD1/PDL1 and other markers by immunohistochemistry, in response to administration of XmAb18087 monotherapy and in combination with pembrolizumab
- PD: immunohistochemistry (IHC) SSTR2 panel
- PD: MCC and SCLC IHC panels
- Correlation of clinical/radiographic response with MCPyV serology (MCC subjects only)
- Additional exploratory genetic, cellular, and/or serum markers of potential future interest. If evidence of therapeutic activity is seen with XmAb18087, biobanked samples may be assessed for genetic and immunologic factors that might predict response or nonresponse (optional part of study and may be reported separately from the clinical study report). Samples will not be retained for more than 15 years.

Statistical Methods:

Analysis Populations:

The populations defined below will be used for analysis:

- **Safety population:** All subjects who are enrolled and receive at least 1 infusion of XmAb18087.
- **Evaluable population:** All subjects who are enrolled, receive at least 1 cycle (Parts A and C: 6 doses XmAb18087, Part B: 5 doses XmAb18087 and 1 dose pembrolizumab) of XmAb18087 and have at least 1 postbaseline RECIST 1.1 assessment of tumor imaging available.
- **PD population:** All subjects who are enrolled, receive at least 1 dose of XmAb18087 (and 1 infusion of pembrolizumab, when relevant for a particular PD assessment), and have at least 1 preinfusion and 1 postinfusion set of biomarker data available for analysis.
- **PK populations:** All subjects who are enrolled and receive at least 1 dose of XmAb18087 (ie, the XmAb18087 PK population) or 1 infusion of pembrolizumab, (ie, the pembrolizumab PK population), and have at least 1 set of postinfusion PK data available for analysis.

Continuous data will be presented using descriptive statistics: number of subjects (N), mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage, where the percentage is presented in brackets to 1 decimal place. Safety and efficacy summaries will be provided for the monotherapy and combination therapy arms separately, as well as for the combined arms.

Date of the Protocol: 18 August 2020

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibody
AE(s)	adverse event(s)
AESC	adverse event of specific concern
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
$AUC_{0-\infty}$	area under the serum concentration-time curve from time zero to infinity
AUC_{0-7}	area under the serum concentration-time curve from time zero to seven days postdose
AUC_t	area under the serum concentration-time curve during a dosing interval (t)
β-hCG	beta human chorionic gonadotropin
bpm	beats per minute
bsAb	bispecific antibody
CAR-T	chimeric antigen receptor T cell
CBC	complete blood count
CFR	Code of Federal Regulations
CL	Clearance
C_{max}	maximum observed serum concentration
$C_{min,ss}$	minimum steady-state concentration
$C_{min[trough]}$	predose or trough concentration
C_{ss}	steady-state concentration
C_{trough}	trough concentration at predose
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DERC	Dose Escalation Review Committee
ECG	Electrocardiogram
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
Fab	antigen-binding fragment of an antibody
FACS	fluorescence-activated cell sorting
Fc	fragment, crystallizable
FcγR	Fc gamma receptor
FDA	US Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma glutamyl transferase
GIST	gastrointestinal stromal tumor
GLP	good laboratory practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HbA1C	glycated hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
FSH	follicle-stimulating hormone
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
ICF	informed consent from
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
Ig	immunoglobulin
IgE	immunoglobulin E
IHC	Immunohistochemistry
IL	Interleukin
IMP(s)	investigational medicinal product(s)
IND	Investigational New Drug Application
IRAE	immune-related adverse event
IRB	Institutional Review Board

IUD	intrauterine device
IV	Intravenous
mAb	monoclonal antibody
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-mental State Examination
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	US National Cancer Institute
NET(s)	neuroendocrine tumor(s)
NETSPOT	Ga-68 DOTATATE PET gallium scanning
NOAEL	no-observed-adverse-effect-level
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PBS	phosphate-buffered saline
PD	pharmacodynamics; progressive disease
PD1	programmed cell death protein 1
PDL1	programmed cell death ligand 1
PDL2	programmed cell death ligand 2
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PI	Principal Investigator
PK	Pharmacokinetics
PO	Orally
PR	partial response
Q6W	every 6 weeks
RBC	red blood cell
RD	recommended dose
RedFlu	red fluorescent protein
RECIST	Response Evaluation Criteria in Solid Tumors
SAE(s)	serious adverse event(s)

SAP	statistical analysis plan
scFv	single-chain variable fragment (immunoglobulin fusion protein)
SCLC	small cell lung cancer
SOC	System Organ Class
SOP(s)	standard operating procedure(s)
SRC	Safety Review Committee
SST	Somatostatin
SSTR	somatostatin receptor
$t_{1/2}$	half-life
TEAE(s)	treatment-emergent AE(s)
TESAE(s)	treatment-emergent SAE(s)
TNF-α	tumor necrosis factor α
t_{max}	time to reach maximum concentration
t_{min}	time of minimum concentration
ULN	upper limit of normal
US	United States
UV	Ultraviolet
Vd	volume of distribution
Vd_{ss}, V_{ss}	steady-state volume of distribution
WBC	white blood cell
%Fluct	steady-state fluctuation in concentrations

5. INTRODUCTION

5.1. Background

5.1.1. Somatostatin and Somatostatin Receptors

Somatostatin (SST), a peptide hormone that is secreted by endocrine and other cells throughout the body, has largely inhibitory effects that are mediated through 5 SST receptor (SSTR) subtypes (1-5). The specific effects of SSTR subtypes are largely due to different distributions and levels of expression within tissues (Barbieri, 2013). SSTR2 is widely expressed in normal tissues and upregulated in many types of tumors (Bronstein-Sitton, 2006; Taniyama, 2005). Like other neuroendocrine tumors, a high proportion of Merkel cell carcinomas (MCC) possesses receptors for somatostatin. In one series of 105 MCC tissue samples from 98 patients, SSTR2a and SSTR5 were expressed in 58 cases (59.2%) and 44 cases (44.9%), respectively. Overall, at least one SSTR subtype was expressed in 75 tumors (76.5%). Expression of SSTR2A, but not SSTR5, was associated with Merkel cell polyomavirus (MCPyV) positivity (Gardair, 2015).

Small cell lung cancer (SCLC), like MCC, often expresses SSTR2, with expression detected by immunohistochemistry (IHC) in patient tumor samples at varying frequencies. Among three different studies, SSTR2 IHC positivity was reported in 11/18 cases (61%; Reubi, 2000), 6/19 cases (32%; Lapa, 2016), and 47/98 cases (48%; Lehman, 2019).

These receptors can also be demonstrated in vivo in both MCC and SCLC by somatostatin receptor-based diagnostic imaging techniques, such as indium-111 pentetreotide single-photon emission computed tomography (SPECT; OctreoScan) or Ga-68 DOTATATE positron emission tomography (PET) gallium scanning (NETSPOT) (Kritikos, 2015; Epstude, 2013; Reisinger, 1998; Lapa, 2016; NETSPOT Package Insert, 2018).

Small series and some case reports have demonstrated success with therapeutic targeting of the SSTR in patients with MCC. This includes radionuclide therapy with yttrium-90-DOTATOC (a somatostatin analog containing the active octapeptide of somatostatin (Meier, 2004); peptide receptor radionuclide therapy with lutetium-177 isotope (Salavati, 2012), the somatostatin analogs lanreotide and octreotide (di Bartolomeo, 1996). Somatostatin analog therapy has also been tested in a limited number of SCLC patients with mixed results (Tartarone, 2016).

5.1.2. Merkel Cell Carcinoma

MCC is a rare, aggressive cutaneous malignancy that predominantly affects older adults and is more common in Caucasians compared with other ethnicities. Risk factors for the disease include ultraviolet exposure and advancing age. Immunosuppression, such as that associated with organ transplant, lymphoproliferative malignancies, or HIV, is also a risk factor for the diagnosis.

The tumor has a propensity for local recurrence and early regional lymph node metastasis. In 2013, the MCC incidence rate was 0.7 cases per 100,000 person-years, corresponding to 2488 cases per year. The incidence increased exponentially with age, from 0.1 to 1.0 to 9.8 (per 100,000 person-years) among age groups 40 to 44 years, 60 to 64 years, and ≥ 85 years, respectively (Paulson, 2018).

MCC pathogenesis is associated with either the presence of MCPyV or chronic exposure to ultraviolet light (UV), which can cause a characteristic pattern of multiple DNA mutations. In areas with high UV exposure, UV-mediated carcinogenesis is predominant; by contrast, in areas with lower UV exposure, the majority of MCC cases are of viral etiology. The 2 etiologies share similar clinical, histopathological, and prognostic characteristics. Ultraviolet light exposure is suspected to be involved in viral-mediated and non-viral-mediated carcinogenesis, by contributing to immunosuppression or DNA damage, respectively (Becker, 2017).

Approximately 30% of patients have locoregional metastases at the time of initial diagnosis. In an analysis of over 9000 MCC cases from the National Cancer Database between 1998 and 2012, patients presented with local disease in 65% of cases, while 26% had regional lymph node involvement and 8% had distant metastases (Harms, 2016).

Excision of the primary tumor is the first-line therapy for locoregional disease, and surgery is frequently combined with radiation therapy to improve locoregional control. However, recurrences of MCC are frequent, even after definitive local and regional therapy, and are associated with a relatively poor prognosis (Eng, 2004).

In general, the management of patients with distant metastases must be individually tailored. While systemic therapy and radiation therapy have until recently been the primary treatment options, surgery may be beneficial in highly selective circumstances for resection of oligometastasis or symptomatic lesions (NCCN Guidelines, 2019).

Until recently, systemic therapy for metastatic MCC consisted of various regimens of cytotoxic chemotherapy, but these treatments have been met with limited success. While a response rate of 55% was observed to a first-line chemotherapeutic regimen (most commonly platinum plus etoposide), the responses were typically not durable, and the median progression-free survival (PFS) was only 3 months (Iyer, 2016; NCCN Guidelines, 2019).

In contrast, immunotherapy with checkpoint inhibitors has shown promise in treating metastatic MCC. Avelumab, an anti-programmed cell death ligand 1 (PDL1)-targeted monoclonal antibody, is approved in the United States to treat patients with metastatic MCC, irrespective of prior therapy. In the JAVELIN Merkel 200 trial, Part A, 88 patients who had received prior cytotoxic chemotherapy were treated with avelumab. With a median follow-up of 2 years, there was a 33% overall response rate (ORR), including 10 complete responses (Kaufman, 2016; Kaufman, 2018; Nghiem, 2018). The 2-year PFS rate was 26%, and the 2-year overall survival rate was 36%. In addition, 2 anti-programmed cell death protein 1 (PD1) monoclonal antibodies, pembrolizumab and nivolumab, have shown evidence of activity in patients with metastatic MCC (Nghiem, 2019; Topalian, 2017).

There are no FDA approved therapies or standard treatments if anti PD1 or anti PDL1 checkpoint inhibitor therapy fails. MCC is an aggressive tumor with high rates of locoregional recurrence and metastatic spread; thus, development of novel therapeutic agents is a significant unmet medical need. XmAb18087 is a bispecific antibody that simultaneously targets a highly expressed somatostatin receptor and CD3, a T cell identifier, bringing together tumor cells and immune effector cells with the idea of activating the immune system to kill tumor cells. Given the medical need and the previous success of immunotherapy in this indication, XmAb18087 should be investigated for treatment of MCC.

5.1.3. Small Cell Lung Cancer

Small cell lung cancer shares several biological and clinical characteristics with MCC that warrant the investigation of XmAb18087 in this indication as well, including SSTR2 expression, responsiveness to immunotherapy, rapid progression, and poor prognosis. Accounting for 15% of all lung cancers, SCLC is, like MCC, a high-grade neuroendocrine tumor with poor clinical outcome. The estimated yearly incidence of small cell lung cancer in 2017 was approximately 30,000 cases in the United States; almost all cases are associated with a history of cigarette smoking (NCCN Guidelines, 2018).

Around 70% of patients with SCLC present with extensive stage, metastatic disease, for which treatment options are palliative. The standard of care for extensive stage SCLC remains combination chemotherapy with various regimens, with a platinum agent plus etoposide being the most commonly used (NCCN Guidelines, 2018, Früh, 2013). Most patients initially benefit from chemotherapy, with response rates of 60 to 70%, but then quickly relapse; the median PFS in this patient population is less than 6 months (Früh, 2013).

Recently, immune checkpoint inhibitors have shown activity in SCLC. Atezolizumab and durvalumab each received FDA approval in combination with chemotherapy for first line treatment of extensive stage SCLC; pembrolizumab and nivolumab are each approved in the US as single agents in the third-line setting. Still, improvements in clinical outcomes have been modest. For example, in the IMpower133 trial, patients who received atezolizumab plus chemotherapy had a median PFS of 5.2 months, compared to 4.3 months for those receiving chemotherapy alone (Horn, 2018). Thus, despite recent advances in the field, there remains a substantial need for better treatment options for extensive-stage SCLC. This high unmet clinical need coupled with the biological features of SCLC warrant investigation of XmAb18087 in this indication.

5.1.4. Therapeutic Bispecific Antibodies

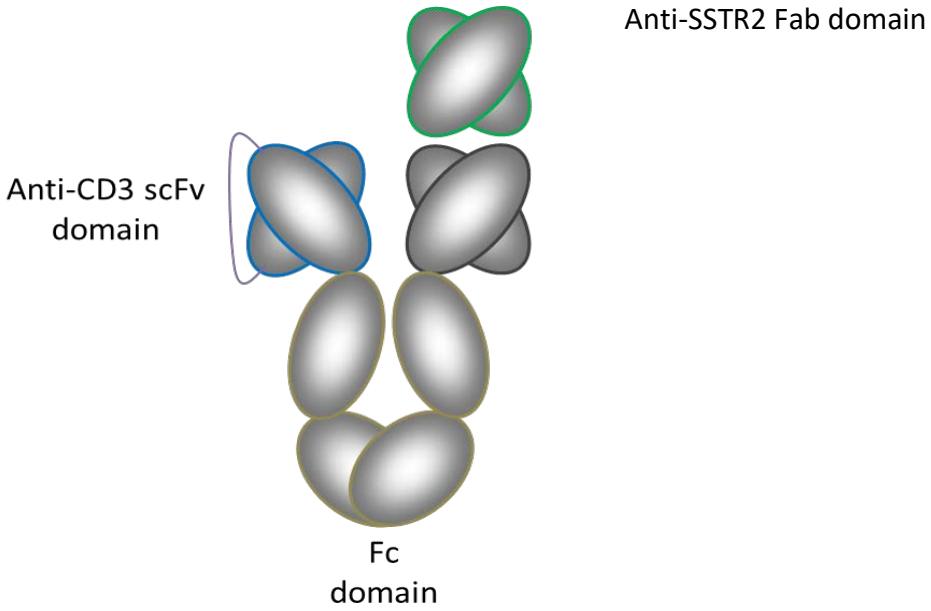
The concept of recombinant antibodies that would allow for simultaneous engagement with 2 targets was first developed in the late 1990s. Bispecific antibodies (bsAbs), it was theorized, could potentially increase binding specificity, providing simultaneous dual activation or blockade of 2 disease mediators, or in the case of cancer therapy, simultaneous binding of cytotoxic T cells and tumor antigens, thus promoting T-cell activation and killing of tumor cells. Although technical obstacles in production initially slowed development of bsAbs, recent advances in protein biology and recombinant expression techniques have resulted in several more easily producible formats for bsAbs, each of which has different properties (Spiess, 2015).While small format bispecific constructs are rapidly excreted and have short half-lives that require continuous infusion for maintenance of efficacious concentrations, XmAb18087 is built on a construct that includes a full fragment, crystallizable (Fc) region, which is designed to yield pharmacokinetics (PK) similar to humanized antibodies and should allow intermittent administration on a weekly or biweekly schedule (Przepiorka, 2015).

5.1.5. XmAb18087 Product Description

XmAb18087 is a humanized bsAb that binds both the tumor antigen SSTR2 and CD3 antigen to recruit cytotoxic T cells for killing of $SSTR2^{+}$ tumor cells. [redacted]

[redacted]

Figure 1. Molecular Domain Format of XmAb18087



Fc = fragment, crystallizable; scFv = single-chain variable fragment (immunoglobulin fusion protein); SSTR = somatostatin receptor.

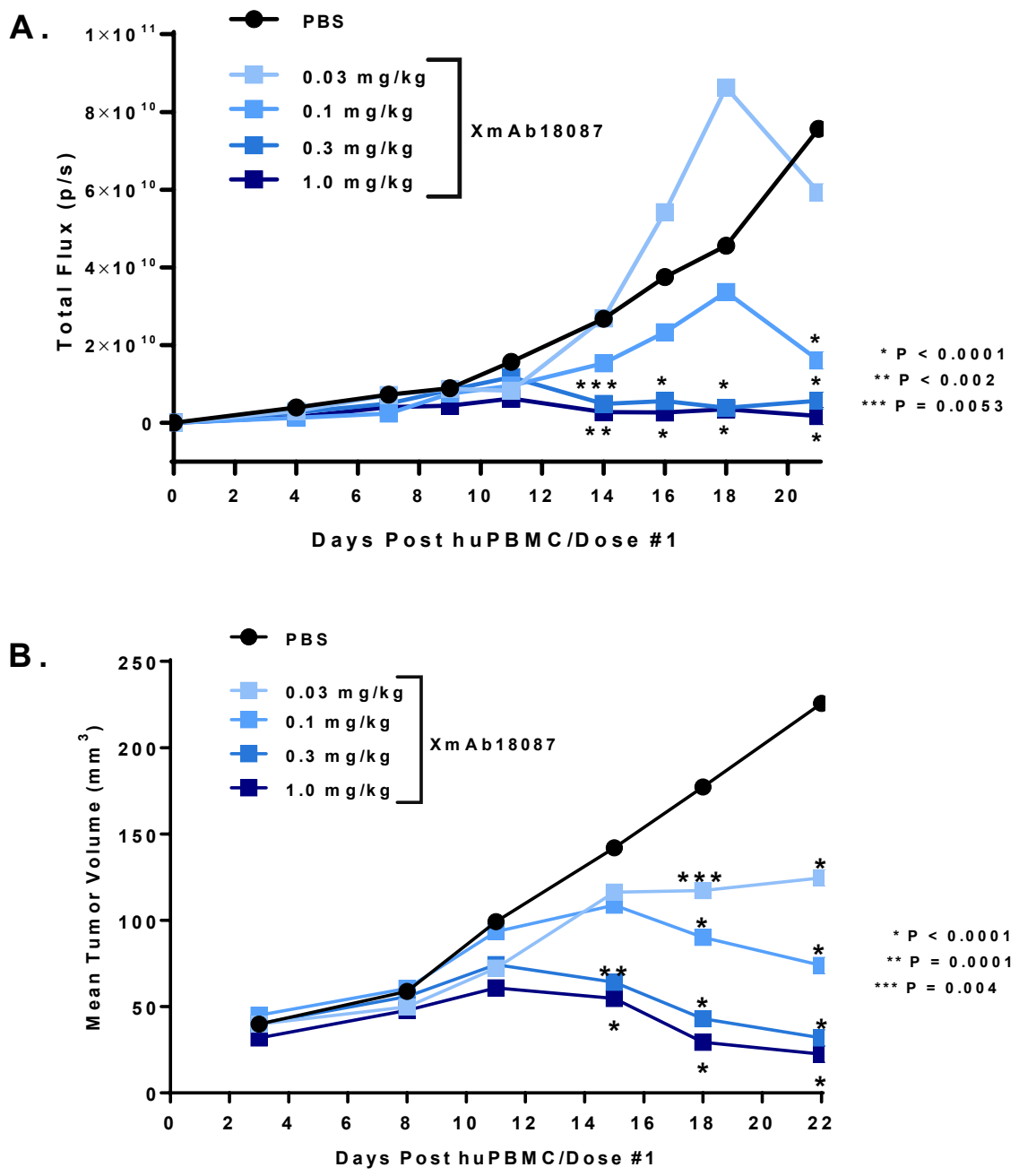
5.1.6. Preclinical Studies

5.1.6.1. Pharmacology

XmAb18087 is a humanized and affinity-optimized bsAb that engages both SSTR2 on tumor cells as well as CD3 on T cells to recruit cytotoxic T cells to kill $SSTR2^+$ tumor cells. XmAb18087 has been designed to maintain full-length humanized monospecific antibody properties in a bispecific antibody, thus enabling the design of stable molecules with favorable in vivo half-life and allowing for standard antibody production methods.

In preclinical in vitro studies, XmAb18087 stimulated robust redirected T-cell–mediated cytotoxicity against $SSTR2^+$ cell lines [redacted]

Figure 2. Antitumor Activity in a Mouse Xenograft Model



huPBMCs = human peripheral blood mononuclear cells; NSG = NOD SCID gamma; PBS = phosphate-buffered saline; FLuc = Firefly Luciferase.

On Study Day 0, young NSG mice received a subcutaneous injection of $1x10^6$ A549 Red-FLuc cells from a human non-small cell lung tumor cell line that had been modified to express a red-shifted luciferase transgene for in vivo imaging. Seven days later, mice were engrafted intraperitoneally with 10×10^6 huPBMCs and treated with either vehicle (PBS), or 0.03, 0.1, 0.3 , or 1.0 mg/kg of XmAb18087 once a week for 3 consecutive weeks. **(A)** Tumor burden was monitored by in vivo imaging using total flux (p/s) captured by In Vivo Imaging System. **(B)** Tumor volumes were determined using physical caliper measurements.

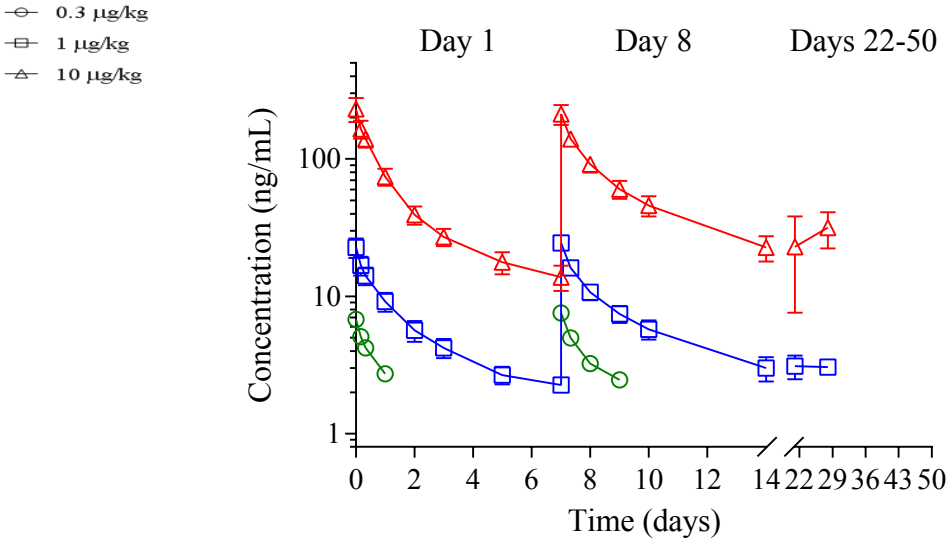
[redacted]

In summary, the results in human cells, in human xenograft in mice, and in cynomolgus monkeys indicate activity of XmAb18087 against SSTR2$^+$ cells and supports clinical assessment of XmAb18087 in SSTR2$^+$ cancers, including neuroendocrine tumors (NET) and gastrointestinal stromal tumor (GIST.)

5.1.6.2. Pharmacokinetics and Toxicokinetics

In a good laboratory practice (GLP) toxicology study, [redacted]

Figure 3. XmAb18087 Mean Serum Concentration Versus Time in Cynomolgus Monkeys (Good Laboratory Practice)



The mean results of a noncompartmental analysis of this study are shown in Table 1.

[redacted]

5.1.6.3. Toxicology

The toxicology of XmAb18087 was also explored in this GLP toxicology study and in 3 non-GLP pharmacology studies.

In the GLP toxicology study, [redacted]

All doses and regimens of XmAb18087 were well tolerated, with no observed effects on food consumption, electrocardiography, body temperature, ophthalmic examinations, or urinalysis

parameters. [redacted]

5.1.7. Human Experience with XmAb18087 and Related Molecules

Two bsAb products have previously been approved by FDA. In 2014, accelerated approval was granted to blinatumomab (Blincyto® PI, 2018) for the treatment of Philadelphia chromosome-negative, relapsed or refractory precursor B-cell acute lymphoblastic leukemia (Przepiorka, 2015). It has since also received approval for treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Blinatumomab is an anti-CD19/anti-CD3 bsAb, constructed as a small-format recombinant protein that, due to its small size, is rapidly cleared and given as a continuous infusion. Cytokine release syndrome and neurologic events were the drug's primary toxicities (Spiess, 2015). In 2017, approval was granted to emicizumab-kxwh (Hemlibra), a bispecific factor IXa- and factor X-directed antibody for prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A. Emicizumab-kxwh is administered by subcutaneous injection. In contrast to blinatumomab, emicizumab-kxwh is not designed to engage T-cells; thus, cytokine release syndrome is not a significant risk with this drug (HEMLIBRA® Package Insert, 2018).

Although the receptor target of XmAb18087 and its distribution are different from those of blinatumomab, the 2 drugs' common mechanism of T-cell engagement and redirection, in addition to the results of Xencor's toxicology studies with XmAb18087 and the company's experience with 2 other CD3-directed bsAb products now in the clinic, indicate that CRS is expected to be a toxicity of the drug, principally after the first dose.

The first-in-human (FIH) Phase 1 clinical study of XmAb18087 in advanced low to intermediate grade NETs and advanced GISTs (XmAb18087-01) has thus far borne out this expectation, with mostly low-grade CRS events being observed. The maximum tolerated dose (MTD)-determining toxicities in the NET arm of the trial were nausea and vomiting. The trial now includes a CRS prophylactic regimen and an antiemetic prophylactic regimen for at least the first [redacted]; these prophylactic regimens decreased the incidence of CRS and the incidence and severity of nausea and vomiting. See also Section 5.3.

5.2. Pembrolizumab

Pembrolizumab (MK-3475; Keytruda®) is a potent humanized immunoglobulin G4 monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PDL1 and programmed cell death ligand 2 (PDL2). Pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab is in clinical development as an IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across several indications, including MCC. For more details on these specific indications, refer to the approved product labeling for detailed background information (Keytruda® Package Insert, 2020).

The clinical responses to pembrolizumab highlight the utility of immunotherapeutic agents for treating cancer. However, some patients either fail to respond to pembrolizumab or relapse after an initial response. Such patients could potentially benefit from the addition of an additional immune-targeted agent with a distinct mechanism of action. This general rationale has spurred the investigation of several T-cell bispecific antibodies in combination with anti-PD1 agents, and supports the proposed combination of XmAb18087 with pembrolizumab in MCC, an indication for which the latter is already FDA-approved (Kobold, 2018; Keytruda® Package Insert, 2020).

5.2.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley, 2005; Hunder, 2008).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PDL1 and/or PDL2; Greenwald, 2005; Okazaki, 2001).

The structure of murine PD1 has been resolved (Zhang, 2004). PD1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic

tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki, 2001; Chemnitz, 2004; Sheppard, 2004; Riley, 2009). As a consequence, the PD1/PDL1 pathway is an attractive target for therapeutic intervention in a number of neoplastic diseases.

5.2.2. Nonclinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PDL1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Blank, 2004; Curran, 2010; Hirano, 2005; Pilon-Thomas, 2010; Strome, 2003; Spranger, 2014; Weber, 2010). Antimouse PD1 or antimouse PDL1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia, and colorectal carcinoma (Curran, 2010; Nomi, 2007; Pilon-Thomas, 2010; Strome, 2003; Zhang, 2004). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B, and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T-cell function in vivo (Curran, 2010). Experiments have confirmed the in vivo efficacy of antimouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models.

5.2.3. Justification for Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 400 mg every 6 weeks (Q6W), which is a current FDA-approved dose for adults with recurrent locally advanced or metastatic MCC (Keytruda® Package Insert, 2020).

5.3. Rationale for Dose Selection of XmAb18087-01 FIH, XmAb18087-02, and Study Design

[redacted]

6. STUDY OBJECTIVES

6.1. Primary Objectives

The primary objectives of the study are as follows:

1. To determine the safety and efficacy (by ORR, complete response [CR], and partial response [PR] per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) of XmAb18087 monotherapy in subjects with advanced MCC that has progressed after treatment with standard therapies
2. To determine the safety and efficacy (by ORR, CR, and PR per RECIST 1.1 criteria) of XmAb18087 in combination with pembrolizumab in subjects with advanced MCC who have not received prior anti-PD1 or anti-PDL1 therapies, and for whom pembrolizumab as a single agent is indicated
3. To determine the safety and efficacy (by ORR, CR, and PR per RECIST 1.1 criteria) of XmAb18087 monotherapy in subjects with extensive-stage SCLC that has progressed after treatment with standard therapies

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

1. To assess antitumor activity of XmAb18087 by PFS per RECIST 1.1 criteria, as well as overall survival (OS) and duration of response, when administered with and without pembrolizumab in subjects with advanced MCC, and as monotherapy in subjects with extensive-stage SCLC
2. To characterize the PK and immunogenicity of XmAb18087 administered with and without pembrolizumab in subjects with advanced MCC, and as monotherapy in subjects with extensive-stage SCLC
3. To assess the PK profile (C_{max} and trough concentration, $C_{min[trough]}$) of pembrolizumab when co-administered with XmAb18087

6.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

1. To assess the incidence, timing, and severity of CRS by the following:
    a. CRS-related AEs (incidence and grade of AEs and incidence of serious adverse events [SAEs])
    b. Biomarkers of CRS
2. To characterize the biological activity associated with administration of XmAb18087 with and without pembrolizumab by assessment of cell surface markers on selected immune system cells in peripheral blood, including changes in lymphocyte subsets and in T-cell activation/exhaustion by flow cytometry and similar bioanalytical methods

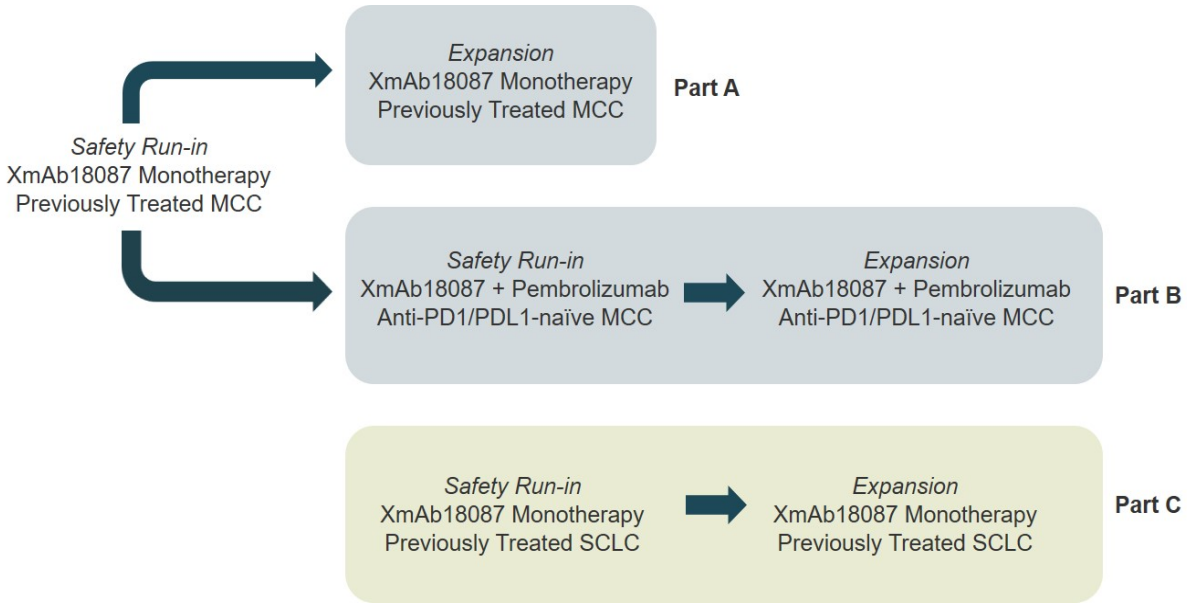
3. To characterize PD by correlation of clinical response with NETSPOT® (gallium 68 dotatate) positron emission tomography/computed tomography (PET/CT) scan results after XmAb18087 administration with and without pembrolizumab
4. To evaluate by immunohistochemistry tumor-cell expression of SSTR2 and PDL1 and tumor-infiltrating T cells expression of proliferation markers and PD1/PDL1 after XmAb18087 administration with and without pembrolizumab, as well as changes in other immune cell subsets
5. To characterize the pharmacodynamic (PD) changes in the intratumoral inflammatory response using immunostaining of immune cells and analysis of RNA signatures
6. To correlate clinical response in MCC subjects to MCPyV status as determined by serology and immunohistochemistry

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a Phase 1b/2, multiple-dose study of XmAb18087, both as a monotherapy and in combination with pembrolizumab in MCC subjects, and as monotherapy only in SCLC subjects. The study is designed in 3 parts, Part A, Part B, and Part C shown in Figure 4.

Figure 4: Study Design



MCC = Merkel cell carcinoma; PD1 = programmed cell death protein 1; PDL1 = programmed cell death ligand 1; SCLC = small cell lung cancer.

Part A is designed to describe safety and efficacy, and to assess PK and immunogenicity of XmAb18087 monotherapy in subjects with advanced MCC. All eligible subjects will have relapsed or refractory disease that has previously been treated with all standard therapies for which they are eligible.

Part A will enroll safety run-in cohorts to confirm the safety and tolerability of XmAb18087 monotherapy administered IV with weekly step-up dosing for 42-day cycles. Additional subjects will then be enrolled into an expansion cohort and will receive XmAb18087 monotherapy using the recommended dose (RD) identified following the safety run-in cohorts.

Part B is designed to describe safety and efficacy, and to assess PK and immunogenicity of XmAb18087 in combination with pembrolizumab in subjects with advanced MCC. All eligible subjects may be treatment naïve or have relapsed or refractory disease after prior treatment; however, subjects who have received prior treatment with anti-PD1 or anti-PDL1 therapeutics will not be eligible to participate in Part B.

Part B will enroll additional safety run-in cohorts to confirm the safety and tolerability of XmAb18087 in combination with pembrolizumab. Subjects will receive step-up IV dosing of XmAb18087 (except for Cohort 1B, in which subjects will receive the same dose level on each

dosing day) on Days 1, 8, 22, 29, and 36, and IV dosing of pembrolizumab on Day 15 of each 42-day cycle. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 plus pembrolizumab combination therapy using the RD identified following the safety run-in.

Enrollment into Part B safety run-in cohorts (starting with Cohort 1B) may begin after the first safety run-in cohort in Part A (Cohort 1A, one dose level higher than Cohort 1B) has completed the first cycle and the regimen has been demonstrated to be tolerable.

Part C is designed to describe safety and efficacy, and to assess PK and immunogenicity of XmAb18087 monotherapy in subjects with extensive-stage SCLC. All eligible subjects will have relapsed or refractory disease that has previously been treated with all standard therapies for which they are eligible.

Part C of the study will enroll additional safety run-in cohorts to confirm the safety and tolerability of XmAb18087 monotherapy in this indication. The safety run-in will follow the same cohort schema as described for Part A to identify a RD for expansion in SCLC. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 monotherapy using the RD identified following the safety run-in.

Enrollment into Part C may begin concurrently with Part A.

Part A, Part B, and Part C: The decision to advance to higher dose levels after each safety run-in cohort will be made by an SRC based on review of the aggregate safety data for all subjects in that cohort as well as cumulative safety data for the study overall. The SRC will be allowed to make adaptations to the dosing schema, if needed, in accordance with evolving trial safety and tolerability findings, as long as adaptations do not significantly increase subject risk. Any such adaptations would require a protocol amendment and IRB approval.

In each safety run-in cohort, no more than 1 subject will receive the first infusion of XmAb18087 on any given day.

Subjects may be admitted and monitored on Day -1 (hospitalization is optional), and will be admitted on study days 1, 2, and 3 for their first dose of XmAb18087 and for at least 48 hours following the second dose. In addition, any subject who has shown symptoms of CRS during inpatient admission will continue to be monitored as an inpatient for at least 24 hours after the symptoms have subsided.

The Schedules of Assessments is provided in Section 7.9, Table 7.

7.2. Study Flowcharts

Figure 5 shows the dosing schedule for each 42-day cycle in the Part A and Part C monotherapy portions of the trial, while Figure 6 shows Part B combination therapy portions of the trial. Inpatient stays are only required in Cycle 1.

Figure 5: Part A and Part C: XmAb18087 Monotherapy Treatment

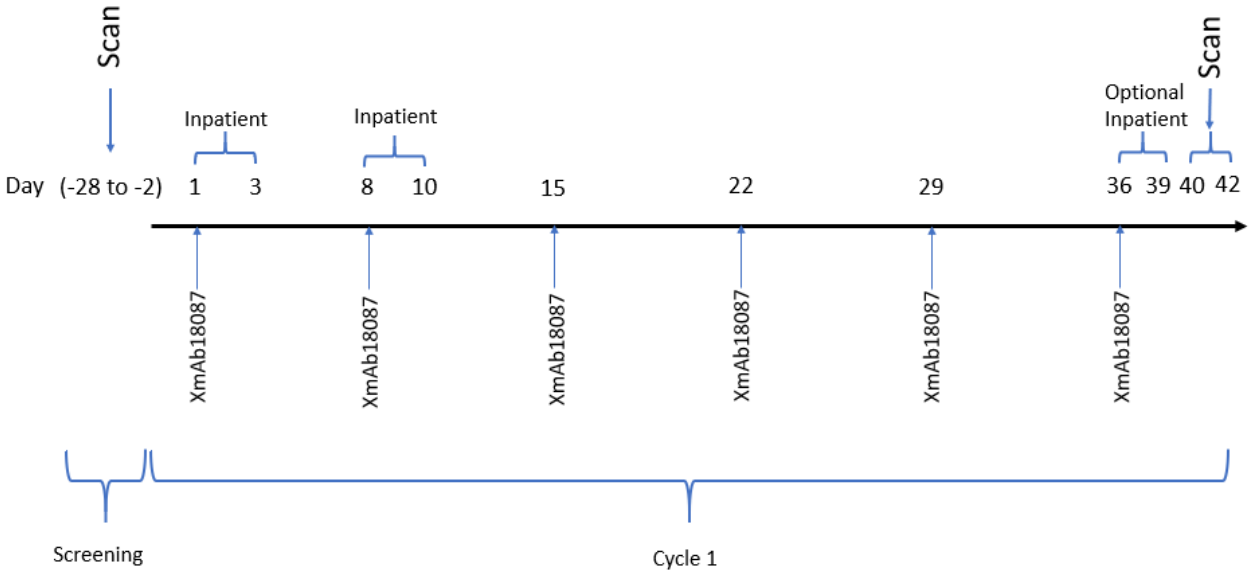
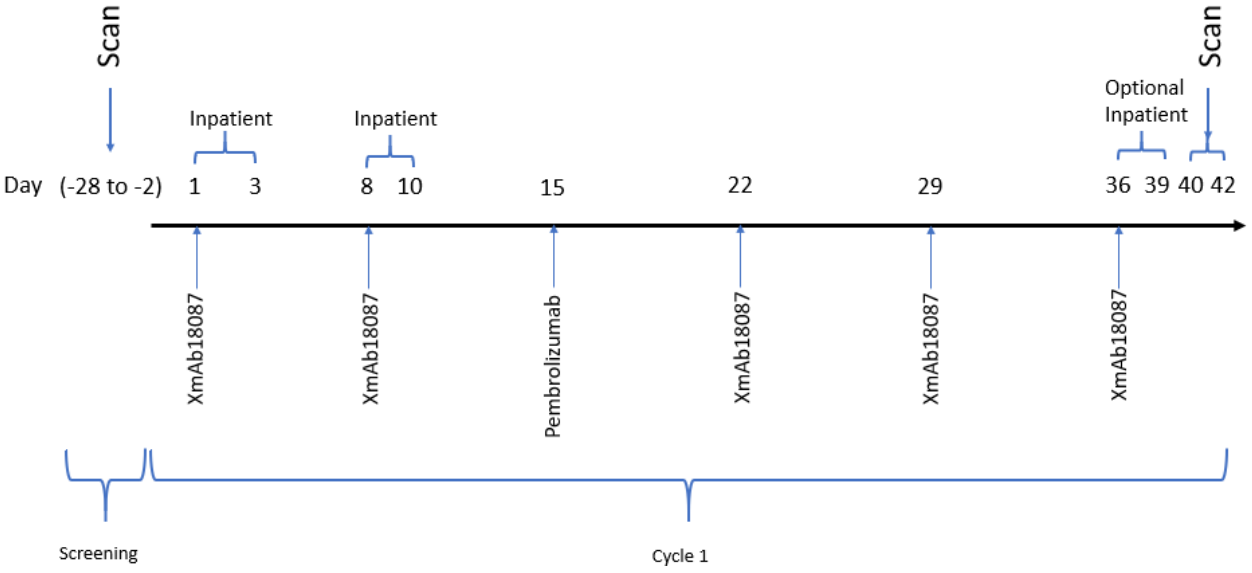


Figure 6: Part B: XmAb18087/Pembrolizumab Combination Therapy Treatment



7.3. Dosing Schedule

Each subject will be administered XmAb18087 IV at a constant infusion rate over [redacted].

The initial treatment period for each subject in this study is 1 cycle. Each cycle is 42 days long. In Part A and Part C, each cycle will consist of 6 weekly doses of XmAb18087 (on Days 1, 8, 15, 22, 29, and 36).

In Part B, each cycle will consist of 5 XmAb18087 doses on Days 1, 8, 22, 29, and 36. Pembrolizumab will be administered as 1 dose during each 42-day cycle, on Day 15.

Part A dose levels are defined in Table 2. Part B dose levels are defined in Table 3. Part C dose levels are defined in Table 4.

The dose is based on the subject's actual baseline weight measurement in kilograms (rounded to the nearest integer) on Day -1. Following the first dose at any dose level, the weight used for calculation of subsequent doses will be modified only if the subject's weight changes by more than 10% from the baseline weight, at which point the dose will be recalculated using the current weight (rounded to the nearest integer).

Table 2: Part A (MCC) Monotherapy Safety Run-in and Expansion Cohorts

	Cycle and Day	Cycle 1							Cycle 2+							Subjects
		D1	D8	D15	D22	D29	D36	D40 ± 2	D1	D8	D15	D22	D29	D36	D40 ± 2	
	Drug	XmAb18087 (µg/kg)						EA	XmAb18087 (µg/kg)						EA	
	Study Day	1	8	15	22	29	36	40	43	50	57	64	71	78	82	
Part A (Safety Run-in)	1A	0.3	**1.0**	1.0	1.0	1.0	1.0	---	1.0	1.0	1.0	1.0	1.0	1.0	---	3 - 6
	2A	0.3	1.0	**2.0**	2.0	2.0	2.0	---	2.0	2.0	2.0	2.0	2.0	2.0	---	3 - 6
	3A	0.3	1.0	2.0	**4.0**	4.0	4.0	---	4.0	4.0	4.0	4.0	4.0	4.0	---	3 - 6
Part A (Expansion)	Expansion A	At RD cohort														Up to 22

D = day; EA = efficacy assessment (no drug administered); MCC = Merkel cell carcinoma; RD = recommended dose. Maximum escalated dose for each cohort in bold.

Table 3: Part B (MCC) Combination Therapy Safety Run-in and Expansion Cohorts

	Cycle and Day	Cycle 1							Cycle 2+							Subjects
		D1	D8	D15	D22	D29	D36	D40 ± 2	D1	D8	D15	D22	D29	D36	D40 ± 2	
	Drug	XmAb18087 (µg/kg)		Pem (mg)	XmAb18087 (µg/kg)			EA	XmAb18087 (µg/kg)		Pem (mg)	XmAb18087 (µg/kg)			EA	
	Study Day	1	8	15	22	29	36	40	43	50	57	64	71	78	82	
Part B (Safety Run-in)	1B	**0.3**	0.3	400	0.3	0.3	0.3	---	0.3	0.3	400	0.3	0.3	0.3	---	3 - 6
	2B	0.3	**1.0**	400	1.0	1.0	1.0	---	1.0	1.0	400	1.0	1.0	1.0	---	3 - 6
	3B	0.3	1.0	400	1.0	**2.0**	2.0	---	2.0	2.0	400	2.0	2.0	2.0	---	3 - 6
	4B	0.3	1.0	400	1.0	2.0	2.0	---	2.0	**4.0**	400	4.0	4.0	4.0	---	3 - 6
Part B (Expansion)	Expansion B	At RD cohort														Up to 30

D = day; EA = efficacy assessment (no drug administered); MCC = Merkel cell carcinoma; Pem = pembrolizumab; RD = recommended dose. Maximum escalated dose for each cohort in bold.

Table 4: Part C (SCLC) Monotherapy Safety Run-in and Expansion Cohorts

	Cycle and Day	Cycle 1							Cycle 2+							Subjects
		D1	D8	D15	D22	D29	D36	D40 ± 2	D1	D8	D15	D22	D29	D36	D40 ± 2	
	Drug	XmAb18087 (µg/kg)						EA	XmAb18087 (µg/kg)						EA	
	Study Day	1	8	15	22	29	36	40	43	50	57	64	71	78	82	
Part C (Safety Run-in)	1C	0.3	**1.0**	1.0	1.0	1.0	1.0	---	1.0	1.0	1.0	1.0	1.0	1.0	---	3 - 6
	2C	0.3	1.0	**2.0**	2.0	2.0	2.0	---	2.0	2.0	2.0	2.0	2.0	2.0	---	3 - 6
	3C	0.3	1.0	2.0	**4.0**	4.0	4.0	---	4.0	4.0	4.0	4.0	4.0	4.0	---	3 - 6
Part C (Expansion)	Expansion C	At RD cohort														Up to 30

D = day; EA = efficacy assessment (no drug administered); RD = recommended dose; SCLC = small cell lung cancer. Maximum escalated dose for each cohort in bold.

7.4. Continuation/Discontinuation of Therapy

There will be a pretreatment tumor assessment, followed by a reassessment after each treatment cycle (Table 7).

7.4.1. Continuation Prior to Progression

Subjects who appear to benefit from XmAb18087 or XmAb18087/pembrolizumab combination therapy may continue to receive additional drug treatment until unacceptable toxicity develops, progression occurs, or the Investigator thinks there is no longer clinical benefit to the subject.

To receive study drug past the first cycle, a subject in Part A or Part C must also satisfy the following criteria:

- Does not meet any criteria for stopping dosing (Section 7.8 and Section 10.3)
- Has recovered from any toxicity to ≤ Grade 2 or to baseline
- Has experienced clinical benefit, as assessed by the Investigator

To receive combination therapy past the first cycle, a subject in Part B must satisfy all continuation criteria for Part A and Part C, and, in addition, must have recovered sufficiently from any immune-related adverse event so that he/she is eligible for continuation/re-initiation of study treatment. Refer to Section 7.4 and the pembrolizumab label (Keytruda® Package Insert, 2020) for dose modification and toxicity management guidelines.

For subjects who continue to receive XmAb18087 or XmAb18087 and pembrolizumab combination therapy past the first cycle, tumor assessments will be repeated after every cycle of therapy.

7.4.2. Continuation/Discontinuation at Progression

Treatment with XmAb18087 as monotherapy (in Part A and Part C) or as part of the combination regimen (in Part B) will be discontinued upon assessment of progressive disease (PD) per RECIST 1.1 (Appendix A).

A subject on combination therapy who is assessed as having PD per RECIST 1.1 may choose to continue pembrolizumab monotherapy in this clinical trial until confirmatory RECIST 1.1 assessment not less than one month and not more than six weeks after the initial determination of PD if he/she

- Meets all the criteria for continuation of dosing listed above in Section 7.4.1
- Has not experienced a decline in Eastern Cooperative Oncology Group (ECOG) performance status since the baseline assessment
- Does not have signs or symptoms of unequivocal PD or PD at disease sites that pose a medical risk to the subject.

Subjects who are assessed as having initial RECIST 1.1 PD but who wish to continue receiving pembrolizumab monotherapy until confirmatory RECIST 1.1 assessment will be reconsented with a separate consent form to ensure they are aware of all treatment options and therapies that they may be foregoing.

If PD is confirmed on follow-up RECIST 1.1 assessment, the subject must discontinue receiving pembrolizumab in this clinical trial.

If PD is not confirmed by follow-up RECIST 1.1 assessment, the subject must discontinue receiving pembrolizumab in this clinical trial but will continue to be followed for progression and survival.

Subjects will be followed as per Table 7, or until death or the initiation of other anticancer therapy (whichever comes first). Information regarding disease status will be collected by the investigational sites for up to an additional 12 months, or until death or disease progression requiring other anticancer therapy (whichever comes first).

7.4.3. Intrasubject Dose Escalation

Intrasubject dose escalation of XmAb18087 is permitted in the study. The subject must meet the following criteria in order to be eligible for treatment at the higher dose level:

- The subject tolerates his/her dose level of XmAb18087
- The subject meets criteria for continuation of therapy prior to progression (Section 7.4.1)
- All subjects in the safety run-in cohort at the next higher dose level have completed the first cycle of treatment, and the SRC has made the decision that the higher dose level is tolerable

No dose escalation will be permitted for pembrolizumab.

For MCC subjects, crossover from monotherapy (Part A) to combination therapy (Part B) is not permitted. Subjects in Part B may not escalate more than once.

7.5. Number of Subjects

Up to 142 subjects will be enrolled; the total number required will depend on the number of safety run-in cohorts required to define each RD for expansion in Part A, Part B, and Part C. Up to 25 clinical investigation sites in the US will enroll subjects in this study.

7.6. Treatment Assignment

Subject Screening Number: Subjects who consent for the study will be assigned a Subject Screening Number.

Subject Enrollment Number: Subjects eligible to receive study treatment will be assigned a Subject Enrollment Number.

Enrolled subjects will be assigned to a cohort as follows:

- Subjects with advanced MCC who have received prior treatment with or are ineligible for treatment with anti-PD1 and/or anti-PDL1 will be assigned to a monotherapy cohort in Part A.
- Subjects with advanced MCC who are anti-PD1 and anti-PDL1 therapy naïve and who do not have a contraindication to anti-PD1 therapy will be assigned to a combination therapy cohort in Part B.

- Subjects with extensive stage SCLC who have received prior treatment with standard therapies will be assigned to a monotherapy cohort in Part C.

7.7. Safety Run-in Cohorts

In each safety run-in cohort, no more than 1 subject will be initiated on treatment with XmAb18087 on any given day.

The planned initial XmAb18087 dose for all cohorts is 0.3 µg/kg. Subsequent doses will then be escalated in steps (except for Cohort 1B, which will use 0.3 µg/kg for all doses) as indicated in Table 2, Table 3, and Table 4 in an effort to reduce the incidence and severity of CRS.

For all safety run-in cohorts in Part A, Part B, and Part C, the SRC will decide whether to advance to the next higher dose level cohort based on review of all available safety data. For each cohort, 3 subjects will be initially enrolled. If no subject experiences an adverse event of specific concern (AESC, as defined in Section 7.8 below), the SRC will be convened after all 3 subjects have completed one treatment cycle or discontinued treatment, whichever comes first. If 1 of the initial 3 subjects experiences an AESC, 3 additional subjects will be enrolled in that cohort (up to a total of 6 subjects) prior to convening the SRC. If 2 subjects experience an AESC, no additional subjects will be enrolled until the SRC has convened and made a recommendation based on the available safety data. Based on the type and severity of toxicities observed, the SRC may modify the safety run-in scheme (eg, decreases in dose level, smaller escalation steps, or other changes in the regimen), as long as the changes do not significantly affect the risk profile of the study.

If a subject discontinues treatment prior to completion of the first cycle due to an AE, that subject will not be replaced. If a subject discontinues treatment prior to completion of the first cycle for any other reason, an additional subject may be enrolled as a replacement.

Part A will begin by enrolling 3 to 6 subjects in Cohort 1A. After Cohort 1A dosing is demonstrated to be tolerable and is approved by the SRC, Part B will begin by enrolling Cohort 1B, which is one dose level lower than Cohort 1A.

Part C may begin concurrently with Part A.

The safety run-in portion will continue until establishment of an RD for expansion or until the repeated dose level reaches the highest dose planned in this study.

Enrolling additional subjects beyond 142 will require a protocol amendment.

7.8. Criteria for Adverse Events of Specific Concern and Dose Adjustment

The National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, will be used for grading toxicities, except for CRS, which will be graded using the CRS revised grading system (Section 11.2 or Appendix C; Lee, 2014).

An AESC is defined as an AE or clinically significant abnormal laboratory value (unless clearly attributable to underlying malignancy or concurrent disease) occurring after the initiation of dosing and meeting the criteria listed below:

For Parts A, B, and C:

1. Any Grade 5 toxicity

2. Grade ≥ 3 thrombocytopenia lasting ≥ 7 days or ≥ Grade 3 thrombocytopenia of any duration if associated with ≥ Grade 3 bleeding
3. Grade 4 neutropenia or Grade 3 febrile neutropenia lasting ≥ 7 days, or Grade 4 febrile neutropenia
4. Any ≥ Grade 3 nonhematological toxicity, **except**:
    a. Grade 3 fatigue, asthenia, fever, anorexia, or constipation
    b. Grade 3 nausea, vomiting, diarrhea, or abdominal pain controlled by medical management that decreases to ≤ Grade 2 within ≤ 7 days
    c. Grade 3 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) that decrease to ≤ Grade 2 within ≤ 5 days
    d. Grade ≥ 3 gamma glutamyl transferase (GGT), unless it occurs with AST, ALT, and/or total bilirubin values that meet AESC criteria
    e. Grade 3 electrolyte abnormalities that are clinically insignificant, or treatable, and that resolve, with or without intervention, to < Grade 2 in < 72 hours
    f. Grade 3 or 4 lipase values that are not accompanied by ≥ Grade 3 amylase values or clinical symptoms or radiographic evidence of pancreatitis

Additional Criterion for Part B (combination therapy) only:

1. Any immune related adverse event (IRAE) that requires permanent discontinuation of study drug according to the guidelines in Table 18

Subjects who experience any toxicity should be followed until the toxicity stabilizes or has returned to their baseline level, or until the commencement of a new anticancer treatment.

Refer to Section 10.3 for safety criteria for adjustment or stopping XmAb18087 and pembrolizumab.

7.8.1. Replacement of Subjects

A subject enrolled in a safety run-in cohort who withdraws from study before completing the first cycle for reasons other than an AE will be considered to have inadequate data for evaluation by the SRC. In such cases, a replacement subject may be enrolled to receive the same dose of XmAb18087 (and pembrolizumab, when applicable) as the subject who withdrew prematurely. Subjects enrolled in the safety run-in cohorts who are discontinued from the study for any reason after the first cycle will not be replaced.

7.8.2. Criteria for Study Termination

Sequential boundaries will be used to monitor AESC rates over the monotherapy expansion cohorts and combination therapy expansion cohorts, separately. If excessive numbers of AESC are seen; that is, if the number of AESC that occur in either expansion cohort is equal to or exceeds a boundary, b_n, out of n subjects (n = all safety-evaluable subjects in the disease-specific expansion cohort [Table 5]), then enrollment will be suspended until the SRC has met.

Table 5: Boundaries for AESC Incidence: Cohort A

Subjects, n of 22	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Boundary, b_n	-	-	3	3	3	4	5	5	6	6	6	7	7	7	8	8	8	8	9	9	9	10

AESC = adverse event of specific concern.
This is a Pocock-type stopping boundary that yields the probability of crossing the boundary of at most 7.5% when the rate of AESC is equal to the acceptable rate of 20% (Ivanova, 2005). If instead the rate of AESC is an excessive 40%, then on average only 14 of the 22 patients will complete the toxicity follow up period before the boundary is crossed.

Table 6: Boundaries for AESC Incidence: Cohorts B and C

Subjects, n of 30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	3	3	4	5	5	6	6	6	7	7	7	8	8	8	6	9	9
Subjects, n of 30	21	22	23	24	25	26	27	28	29	30										
Boundary, b_n	9	10	10	10	11	11	11	11	12	12										

AESC = adverse event of specific concern.
This is a Pocock-type stopping boundary that yields the probability of crossing the boundary of at most 8% when the rate of AESC is equal to the acceptable rate of 20% (Ivanova, 2005). If instead the rate of AESC is an excessive 40%, then on average only 17 of the 30 patients will complete the toxicity follow up period before the boundary is crossed.

If the enrollment of a disease-specific expansion cohort has been suspended in accordance with this section, it may not be reopened until the SRC has met, considered the available data, and made a decision to continue, with or without modifications to the trial.

7.9. Study Assessments

The Schedule of Assessments is shown in Table 7. Pretreatment, treatment, and follow-up procedures are detailed in Sections 7.9.1 through 7.9.5.

Table 7: Schedule of Assessments

Evaluation or Procedure	Pretreatment		Cycle 1													
Study Day	**Screen (-28 to -2)**	**Day -1**	**1**	**2**	**3**	**8**	**9**	**10**	**15**	**22**	**29**	**36**	**37**	**38**	**39**	**40 ± 2**
Informed consent	X															
NETSPOT Gallium 68 dotatate PET/CT scan[a,b]	X															X
Review of inclusion/exclusion criteria	X															
Collection of FFPE tumor sample/slides	X															
Record tumor genetic information	X															
Inpatient status[c,d]		X	X	X	X	X	X	X				X	X	X	X	
XmAb18087 administration[e,f]			X			X			X	X	X	X				
Pembrolizumab administration[f]									X							
Medical history[g]	X	X														
Demographics	X															
Physical examination[g,h]	X	X		X	X	X	X	X	X	X	X	X				X
Neurologic examination[i]		X														
Vital signs[c,j,k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X														
Weight		X	X			X			X	X	X	X				
ECOG performance status[h]	X	X	X			X			X	X	X	X				
12-lead electrocardiogram (supine)[l,m]	X	X	X			X	X		X	X	X	X				
CBC w/ differential (absolute and percentage), platelet count[h]	X		X	X	X	X	X	X	X	X	X	X				
Chemistry panel[h]	X		X	X	X	X	X	X	X	X	X	X				
Coagulation panel[h]	X		X	X		X		X	X	X	X	X				
Urinalysis	X	X		X		X		X	X	X	X	X				
HBsAg, HBcAb, HCV, HIV	X															

Table 7: Schedule of Assessments (Continued)

Evaluation or Procedure	Pretreatment		Cycle 1													
Study Day	**Screen (-28 to -2)**	**Day -1**	**1**	**2**	**3**	**8**	**9**	**10**	**15**	**22**	**29**	**36**	**37**	**38**	**39**	**40 ± 2**
Serum β–hCG (females of childbearing potential) FSH (postmenopausal)[n]	X	X								X						
Flow cytometry (blood)[o]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Cytokine/inflammation panel[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Polyoma virus assay (serum)[q]		X														
Biobanking sample (blood)[r,s]		X		X		X										X
PK blood sampling[t]		X	X	X	X	X		X	X	X	X	X	X	X	X	
Immunogenicity (ADA) blood sampling[u]		X	X			X			X	X	X	X				
RECIST 1.1 tumor assessment[v]	X															X
Monitor/record adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fresh tumor biopsy (optional)[s,w]	X							X								

Table 7: Schedule of Assessments (Continued)

Evaluation or Procedure	Cycle 2 and Higher						
Study Day	**1**	**8**	**15**	**22**	**29**	**36**	**40 ± 2**
NETSPOT Gallium 68 dotatate PET/CT scan[a,b]							X
XmAb18087 administration[e,f]	X	X	X	X	X	X	
Pembrolizumab administration[f]			X				
Physical examination	X	X	X	X	X	X	
Vital signs[j, k]	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	
ECOG performance status[h]	X	X	X	X	X	X	
12-lead electrocardiogram (supine) [l,m]	X	X	X	X	X	X	
CBC w/ differential (absolute and percentage), platelet count[h]	X	X	X	X	X	X	
Chemistry panel[h]	X	X	X	X	X	X	
Coagulation panel[hl]	X	X	X	X	X	X	
Urinalysis	X			X			
Serum β–hCG (females of childbearing potential) FSH (postmenopausal)[n]	X			X			
Flow cytometry (blood)[o]				X		X	
Cytokine/inflammation panel[p]	X			X			
PK blood sampling[t]	X		X				
Immunogenicity (ADA) blood sampling[u,x]	X		X	X		X	
RECIST 1.1 tumor assessment[v]							X
Monitor/record adverse events	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	

Table 7: Schedule of Assessments (Continued)

Evaluation or Procedure	Post-treatment			
Study Day	**EOT**	**14 d post-EOT**	**28 d post-EOT**	**Long-term Follow-up (6 & 12 mo after EOT)**
NETSPOT Gallium 68 dotatate PET/CT scan[a,b]	X			
Medical history			X	
Physical examination	X	X	X	
Vital signs[j, k]	X	X	X	
Weight	X	X	X	
ECOG performance status[h]	X	X	X	
12-lead electrocardiogram (supine) [l,m]			X	
CBC w/ differential (absolute and percentage), platelet count[h]	X	X	X	
Chemistry panel[h]	X	X	X	
Coagulation panel[h]	X	X	X	
Urinalysis	X	X	X	
HBsAg, HBcAb, HCV, HIV	X			
Serum β–hCG (females of childbearing potential) FSH (postmenopausal)[n]	X		X	
Flow cytometry (blood)[o]	X	X	X	
Cytokine/inflammation panel[p]				
Polyoma virus assay (serum)[q]	X		X	
PK blood sampling[t]	X	X	X	
Immunogenicity (ADA) blood sampling[u,x]	X	X	X	
RECIST 1.1 tumor assessment[v]	X			
Monitor/record adverse events	X	X	X	
Concomitant medications	X	X	X	
Phone/email/mail contact for progression				X

Abbreviations: ADA = anti-drug antibody; β–hCG = beta unit of human chorionic gonadotrophin; CBC = complete blood counts; CT = computed tomography; EOI = end of infusion. EOT = end of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACS = fluorescence-activated cell sorting; FFPE = fresh frozen paraffin-embedded; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCV = hepatitis C virus; HIV = human immunodeficiency virus; mo = month; MRI = magnetic resonance imaging; NET = neuroendocrine tumors; PE = physical examination; PET = positron emission tomography; PK = pharmacokinetic; RECIST = Response Evaluation Criteria In Solid Tumors; SSTR2 = somatostatin receptor 2.

[a] If subject has undergone NETSPOT gallium 68 dotatate PET/CT scan within 6 weeks prior to enrollment and the images and a report of results are available for collection, the scan need not be repeated at baseline. If SSTR2 radionuclide scanning and RECIST 1.1 tumor assessment by CT/MRI are planned within 2 days of each other, RECIST imaging should be conducted first.

[b] NETSPOT gallium 68 dotatate PET/CT scan will be performed on Day 40 ± 2 of Cycle 1 and of every second cycle thereafter; that is, at the end of Cycle 3, Cycle 5, etc. The EOT scan will be performed only if the subject has not undergone scan within the past 2 months.

[c] On Day -1, hospitalization is optional. Hospitalization on Days 36 through 39 in Cycle 1 is optional if PK sampling cannot be accommodated as an outpatient. Vital sign assessments on Days 36 through 39 in Cycle 1 will be performed only if the subject is hospitalized.

[d] Any subject who has shown symptoms of CRS during a required inpatient hospitalization will be monitored as an inpatient for at least 24 hours after the symptoms have subsided.

[e] XmAb18087 will be administered as [redacted]. Subjects will be observed as inpatients for the first 2 doses. For all other infusions of XmAb18087, the subject will be observed for at least 4 hours following subsequent infusions, except that the observation period may be decreased to 2 hours if no infusion reactions have occurred for at least 3 consecutive infusions and the subject has completed 4 infusions at the highest dose for that subject.

[f] XmAb18087 is administered on Day 15 in Parts A and C only. Pembrolizumab is administered on Day 15 of each cycle in Part B only. XmAb18087 is NOT to be administered on Day 15 in Part B. Pembrolizumab will be provided by sites as standard of care.

[g] Complete medical history and PE is to be performed at Screening. For all the other time points, only an abbreviated, symptom-directed PE is to be performed.

[h] May be performed up to 24 hours prior to infusion. The following procedures that are completed on Day -1 within 24 hours of Cycle 1 Day 1 dosing do not need to be repeated on Cycle 1 Day 1: PE, ECOG, and local safety laboratories (eg, CBC with differential and platelets, chemistry panel, coagulation panel, and urinalysis). These safety laboratory assessments will be performed by the central laboratory and should also be performed by local clinical site laboratories so that clinical site personnel can review results before administering XmAb18087.

[i] Baseline neurologic examination to be performed on Day -1. If a subject appears to be experiencing neurologic toxicity, the neurologic examination should be repeated as necessary to evaluate the subject's condition. Guidelines on management of neurologic toxicity are included in both Section 11.3.3.4 and Appendix C.

[j] Supine blood pressure and pulse rate, body temperature, respiratory rate, and blood oxygen saturation by pulse oximetry. On days of XmAb18087 infusions, vital signs should be taken within 60 minutes of predose; 15, 30, and 60 minutes after start of infusion (± 5 minutes for each time point); immediately (within 5 minutes) before EOI; 15, 30, and 60 minutes after EOI (± 5 minutes for each time point); and then hourly (± 5 minutes) for 3 hours. When possible, vitals should be measured before blood sampling. Oxygen saturation levels will be captured with each vital sign collection; however, pulse oximetry monitoring must be maintained continuously throughout the entire admission or observation period for each administration of XmAb18087. For information on management of oxygen saturation of 90% or lower, see Section 11.3.3.1. All vital signs during infusion should be taken with the subject in the same position. On nondosing days, vitals should be measured before blood sampling.

[k] On days of pembrolizumab infusions, vital signs should be taken immediately prior (within 10 minutes before blood sampling) to the start of infusion; during the infusion at 5 and 15 minutes (± 2 minutes); immediately (within 2 minutes) before the EOI; and at 15 minutes (± 2 minutes) after EOI.

[l] On days when XmAb18087 is infused, electrocardiograms should be taken prior to infusion, 2 to 4 hours after EOI, and if clinically indicated.

[m] Part B only: ECGs are not performed on days when pembrolizumab is administered.

[n] Once postmenopausal status has been established by FSH, this test need not be repeated during the clinical trial.

[o] In **Cycle 1**, whole blood for flow cytometry (FACS) analysis will be obtained predose on Day 1 (± 1 hour); on Day 2 (24 hours post-EOI ± 3 hours); on Day 3 (48 hours post-EOI ± 3 hours); predose on Day 8 ± 1 hour; on Day 9 (24 hours post-EOI ± 3 hours); on Day 10 (48 hours post-EOI ± 3 hours); predose on Day 15 ± 1 hour; predose on Day 22 ± 1 hour; predose on Day 29 ± 1 hour; predose on Day 36 ± 1 hour; on Day 37 (24 hours post-EOI ± 3 hours); on

Day 38 (48 hours post-EOI ± 3 hours); and on Day 39 (72 hours post-EOI ± 3 hours). In **Cycles 2 and higher**, whole blood for FACS will be obtained predose on Day 22 ± 2 days and on Day 36 ± 2 days. **Upon discontinuation from the study**, whole blood for FACS analysis should be obtained at EOT (± 2 days), at 14 days post-EOT (± 2 days), and at the 28 days post-EOT visit(± 2 days.)

[p] In **Cycle 1**, serum for cytokine profile analysis will be obtained predose on Day 1, 8, and 36 and at 5 minutes (± 1 minute), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), 7 hours (± 10 minutes), and 10 hours (± 10 minutes) post-EOI; on Days 2, 9, and 37 (24 hours post-EOI ± 3 hours), Day 3, 10, and 38 (48 hours post-EOI ± 3 hours), and on Day 39 (72 hours post-EOI ± 3 hours). Additionally, samples will be collected predose on Days 15, 22, and 29 and at 5 minutes (± 1 minute), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), and 7 hours (± 10 minutes) post EOI. In **Cycle 2 and higher**, serum for cytokine profile analysis will be obtained on Day 1 and Day 22 (± 2 days) of each cycle predose and at 1 hour (± 10 minutes), 2 hours (± 10 minutes), and 4 hours (± 10 minutes) post EOI. Serum should also be drawn at any time there is clinical suspicion of cytokine release syndrome and repeated 4 hours later.

[q] Polyoma virus assay serum collection is for Part A and Part B only.

[r] Including serum, peripheral blood, and nucleic acid samples.

[s] Optional; by specific subject consent.

[t] In **Cycle 1**, serum for PK analysis will be obtained at Day -1; on Days 1 and 36 predose and at 5 minutes (± 1 minute), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), 7 hours (± 10 minutes), and 10 hours post-EOI (± 10 minutes, Day 1 only); on Days 2 and 37 (24 hours post-EOI ± 3 hours), and Days 3 and 38 (48 hours post-EOI ± 3 hours), and Day 39 (72 hours post-EOI ± 3 hours); on Day 8 predose and at 5 minutes (± 1 minute) post-EOI; on Day 10 (48 hours post-EOI); and on Days 15, 22, and 29 predose and at 5 minutes post-EOI (± 1 minute). In **Cycles 2 and higher**, serum for PK analysis will be collected on the first day of each cycle (± 2 days) predose and 5 minutes (± 1 minute) post-EOI (all subjects). Subjects in Part B only (combination therapy) will also have serum collected for PK analysis on Day 15 at predose and 5 minutes (± 1 minute) post-EOI. Upon **discontinuation from the study**, serum for PK analysis should be obtained at the EOT visit (± 2 days), the 14-day post-EOT visit (± 2 days), and the 28 day post-EOT visit (± 2 days).

[u] In **Cycle 1**, serum for ADA will be collected on Day -1 and predose (± 1 hour) on Days 1, 8, 15, 22, 29, and 36. In **Cycles 2 and higher**, serum for ADA analysis will be collected predose on Days 1, 15, 22 and 36 (± 2 days). Upon **discontinuation from the study**, serum for ADA will be collected at EOT (± 2 days), at 14 days post-EOT (± 2 days), and at 28 days post-EOT (± 2 days).

[v] Radiographic tumor evaluation will be performed by CT/MRI at baseline and at all other disease assessment time points. All studies for the baseline RECIST assessment should be performed within 14 days prior to the first dose of drug. The EOT tumor assessment will not be performed if the subject has had an assessment within the past 30 days.

[w] The post-treatment fresh tumor biopsy should be performed between 12 and 21 days after first dose of XmAb18087.

[x] Subjects with a positive ADA at termination will be followed every 28 days (± 3 days) until ADA reverts to baseline or until the next intervening treatment.

7.9.1. Pretreatment Evaluations

Only those subjects who meet all inclusion (Sections 8.1 and 8.2) and no exclusion (Sections 8.6 and 8.7) criteria specified may be enrolled into this study. Prior to the initiation of any on-study testing, including screening testing, the subject must have signed the ICF and received a Subject Screening Number (Section 7.6). The pretreatment period lasts for up to 28 days and includes screening evaluations (Day -28 to -2) and baseline assessments (defined as the assessment immediately prior to the first dose).

Prior to administration of XmAb18087, each subject must have completed all screening activities and received approval via the eligibility checklist from the Medical Monitor.

7.9.1.1. Screening Period (Day -28 to -2)

Subjects will undergo a Screening Visit 2 to 28 days prior to the planned first day of study treatment. Screening assessments are as follows:

- Obtain signed informed consent (Section 17.3)
- Review inclusion and exclusion criteria (Sections 8.1, 8.2, 8.6, and 8.7)
- Medical history
- Demographics
- Physical examination (PE; Section 11.7)
- Collect formalin-fixed paraffin embedded (FFPE) tumor sample or slides for immunohistochemical assessment of MCPyV status (MCC subjects only), tumor cell SSTR2 expression and immune cell expression of proliferation and exhaustion markers
- Perform tumor assessment by CT/magnetic resonance imaging (MRI) per RECIST 1.1 criteria and guidelines (Appendix A) within 14 days prior to the first dose of drug
- Perform NETSPOT gallium 68 dotatate PET/CT if not performed within 3 months prior to enrollment (refer to study manual for details on performing NETSPOT gallium 68 dotatate PET/CT). If the subject has undergone NETSPOT gallium 68 dotatate PET/CT scan within 3 months prior to enrollment and the images and reports of results are available, the scan need not be repeated at baseline; however, a copy of images and the report of scan results must be collected.
- Record any available genetic information on the tumor, including sequencing data
- ECOG performance status (Appendix B)
- Vital signs (Section 11.8)
- Electrocardiogram (ECG) standard 12-lead, supine position (Section 11.6)
- Complete blood count (CBC; Section 11.5)
- Chemistry panel (Section 11.5)
- Coagulation panel (Section 11.5)

- Screening test for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb; a subject whose HBsAg is negative and HBcAb is positive may be enrolled if a hepatitis B virus [HBV] DNA test is negative and either the subject is treated with potent antiviral therapy or is retested for HBsAg and HBV DNA every month while on study drug treatment).
- Screening tests for human immunodeficiency virus (HIV) and hepatitis C virus (HCV)
- Serum beta human chorionic gonadotropin (β-hCG) pregnancy test for women of childbearing potential or follicle-stimulating hormone (FSH) for postmenopausal women (Section 11.5)
- Urinalysis (Section 11.5)
- Record concomitant medications (Section 9.2)
- Record adverse events (using CTCAE and CRS revised grading system for grading; Section 11.1)
- Pretreatment fresh tumor biopsy (optional; by specific subject consent) to be examined by fluorescent immunohistochemical assay for tumor-cell expression of SSTR2 and tumor and immune-cell expression of proliferation and exhaustion markers, and by Nanostring analysis of nucleic acid and protein content

7.9.1.2. Baseline Assessments (Day -1 or 1)

If a test or assessment is performed on both Day -1 and Day 1, the Day 1 (predose) test is considered the baseline:

- Medical history
- Abbreviated PE (Section 11.7)
- Neurological examination
- ECOG performance status (Appendix B)
- Vital signs (Section 11.8)
- Height, weight
- ECG: standard 12-lead, supine position (Section 11.6)
- CBC (Section 11.5)
- Chemistry panel (Section 11.5)
- Coagulation panel (Section 11.5)
- Urinalysis (Section 11.5)
- Urine β-hCG pregnancy test for women of childbearing potential (Section 11.5)
- Blood for cell surface markers by flow cytometry or other similar bioanalytical methods (Section 13.3)
- Serum for MCPyV assay (Part A and Part B only)

- PK, cytokine/inflammation panel blood sample (Section 13.1)
- Immunogenicity (ADA) blood sample (Section 13.1)
- Blood for biobanking (Section 13.4)
- Record concomitant medications (Section 9.2) and AEs

7.9.2. Subject Enrollment

Subjects who have completed screening activities and whose eligibility has been confirmed by the Medical Monitor will be considered enrolled in the study.

7.9.3. Treatment Cycle Assessments

The schedule of required procedures and clinical site study days for each cycle are detailed in the Schedule of Assessments (Table 7). The day prior to Cycle 1 Day 1 is Day -1.

Subjects will be followed for PFS and overall survival at 6 and 12 months after end of treatment (EOT) by telephone, email, or mail contact from the clinical site (Section 7.9.5).

Procedures during the treatment cycles to 4 weeks after EOT are detailed in Sections 7.9.3.1 to 7.9.3.2. Study days for required procedures are specified in the Schedule of Assessments (Table 7).

7.9.3.1. Clinical Assessments

PEs and laboratory evaluations may be performed within 24 hours prior to XmAb18087 infusion:

- Record concomitant medications and AEs (CTCAE and CRS revised grading system, Section 11.1).
- Abbreviated, symptom-directed PE, including weight
- ECOG performance status (Appendix B)
- Vital signs (Section 11.8):
  - On infusion days, time points include: within 60 minutes of predose; approximately 15, 30, and 60 minutes after start of infusion (± 5 minutes for each time point); immediately (within 5 minutes) before end of infusion (EOI; if different than 60 minutes from start of infusion); approximately 15, 30, and 60 minutes after EOI (± 5 minutes for each time point); and then hourly (± 5 minutes) for 3 hours. The pulse oximetry for blood oxygen saturation level needs to be captured with each vital sign collection; however, pulse oximetry monitoring must be maintained continuously throughout the entire admission or observation period for each administration of XmAb18087. For information on management of oxygen saturation of 90% or lower, see Section 11.3.3.1.
  - On non-dosing days, vitals should be measured before blood is drawn.
  - For subjects who tolerate 3 XmAb18087 consecutive infusions without an infusion reaction during the infusion or postinfusion observation period and who have completed 4 infusions at the highest dose for that subject, the postinfusion

observation period and vital signs assessment may be reduced from 4 hours to 2 hours.

7.9.3.2. Laboratory Assessments

Unless otherwise specified, assessments during Cycle 1, Days 1, 8, 15, 22, 29, and 36 should be completed ± 1 hour of the scheduled time; for other days during Cycle 1, ± 3 hours; and for subsequent cycles and disease assessments, ± 2 days. Details for laboratory assessments are provided in Section 11.5 and Section 11.6; details for PK, PD, flow cytometry, and biobanking are provided in Section 13.

Laboratory assessments include the following:

- CBC
- Chemistry panel
- Coagulation panel
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Blood for cell surface markers by flow cytometry or similar bioanalytical methods (see the Laboratory Manual for detailed instructions)
- PK (see the Laboratory Manual for detailed instructions)
- Cytokine/inflammation panel (see the Laboratory Manual for detailed instructions)
- ADA blood sample (see the Laboratory Manual for detailed instructions)
- Biobanking blood sample (optional; by specific subject consent)
- ECG, standard 12-lead
- RECIST 1.1 tumor assessment by CT/MRI (See Appendix A)
- Post-treatment fresh tumor biopsy (optional; by specific subject consent) to be examined by various immunohistochemistry assays for tumor-cell expression of SSTR2 and tumor- and immune-cell expression of proliferation and exhaustion markers, and transcriptomic analysis by Nanostring. The optional post-treatment fresh tumor biopsy should be performed between 12 and 21 days after the first dose of XmAb18087.
- NETSPOT gallium 68 dotatate PET/CT after the first cycle of treatment and, for subjects continuing to receive study drug, after every second cycle thereafter NETSPOT gallium 68 dotatate PET/CT should be performed after RECIST tumor assessment by CT/MRI has been completed. Refer to study manual for details on performing NETSPOT gallium 68 dotatate PET/CT.

7.9.3.3. End-of-Treatment Visit

Subjects will have their EOT visit at the end of the last cycle of treatment. If a subject terminates before the end of a cycle, the EOT assessments (Table 7, Schedule of Assessments) will be performed on the day of study termination.

Subjects with a positive ADA at study termination will be followed every 28 days (± 3 days), if feasible, until administration of another anticancer therapy, or until ADA levels return to baseline if results are available.

7.9.4. Post-treatment Follow-up Period (2 Weeks and 4 Weeks After EOT)

Subjects will have visits 14 days post-EOT and 28 days post-EOT. Assessments are as indicated in Table 7. Once these two visits have been completed, the subject will be considered as having completed participation in the clinical trial. If a subject enrolls into another trial or requires treatment before either of these scheduled visits, the visits may be performed earlier. If a subject is unable to return for any scheduled visits after the end of treatment, he/she will be considered as having completed study requirements at the end of treatment.

7.9.5. Long-Term Follow-up Period (6 and 12 Months After EOT)

Subjects will be contacted by site staff by telephone, email, or mail at 6 and 12 months after their active participation in the study ends to gather information about disease progression and survival. Completion of the long-term follow-up period is not required for a subject to be considered as having completed the clinical trial.

7.10. Discussion of Study Design

This is a Phase 1b/2, multiple-dose study designed to describe safety and efficacy, and to assess PK and immunogenicity of XmAb18087 monotherapy and in combination with pembrolizumab in subjects with metastatic MCC or locoregional MCC that has recurred after locoregional therapy with surgery and/or radiation therapy, and XmAb18087 monotherapy in subjects with extensive-stage SCLC that has progressed after standard therapies.

Part A of the study will enroll safety run-in cohorts of subjects with advanced MCC that has progressed after treatment with standard therapies to confirm the safety and tolerability of XmAb18087 monotherapy administered IV with weekly step-up dosing for 42-day cycles. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 monotherapy using the RD identified following the safety run-in.

Part B of the study will enroll safety run-in cohorts of subjects with advanced MCC not previously treated with anti-PD1 or anti-PDL1 agents, and for whom pembrolizumab as a single agent is indicated, to confirm the safety and tolerability of XmAb18087 in combination with pembrolizumab. Subjects will receive step-up IV dosing of XmAb18087 on Days 1, 8, 22, 29, and 36, and IV dosing of pembrolizumab on Day 15 of each 42-day cycle. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 plus pembrolizumab combination therapy using the RD identified following the safety run-in.

Enrollment into the first safety run-in cohort of Part B (Cohort 1B) may begin after the first safety run-in cohort in Part A (Cohort 1A, one dose level higher than Cohort 1B) has completed the first cycle and the regimen has been demonstrated to be tolerable.

Part C of the study will enroll safety run-in cohorts of subjects with extensive-stage SCLC that has progressed after treatment with standard therapies to confirm the safety and tolerability XmAb18087 monotherapy. The safety run-in will follow the same cohort schema as described for Part A to identify a RD for expansion in SCLC. Additional subjects will be enrolled into an expansion cohort and will receive XmAb18087 monotherapy using the RD identified following the safety run-in.

Enrollment into Part C may begin concurrently with Part A.

7.10.1. Risk/Benefit and Ethical Assessment

XmAb18087 has been characterized through an extensive program of in vitro and in vivo testing which demonstrates that the drug binds CD3 and SSTR2 and is active against $SSTR2^+$ cells and tumors. The pharmacology and toxicology of the drug have also been studied in numerous experiments using cynomolgus monkeys, the relevant species for a CD3-directed bsAb. Pharmacology results show that XmAb18087 activates T cells, and toxicology results, as well as results from the first 42 subjects dosed in the XmAb18087-01 trial, indicate that the drug can be administered safely within the careful program of prophylactic medication, frequent subject assessment, and close observation that the XmAb18087-02 clinical trial protocol describes. Given that Part A and Part C of the XmAb18087-02 trial are being conducted in subjects with advanced cancer for which there is no effective available therapy, the sponsor believes that the administration of monotherapy under the auspices of this clinical study is ethical.

Pembrolizumab (Keytruda®) is approved for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC. Given that the combination of XmAb18087 and pembrolizumab will be administered to this patient population within a careful program of frequent subject assessment and close observation, the Sponsor believes that the proposed combination therapy portion of the clinical study is ethical.

7.10.2. Termination of Study

If the Investigator or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects should the clinical study continue, the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study also may be terminated at the Sponsor's discretion, also in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study.
- Failure to enroll subjects at the required rate.
- A decision of the Sponsor to suspend or discontinue development of the IMP.

Should the study be terminated and/or the site closed for whatever reason, all documentation pertaining to the study and IMP must be returned to the Sponsor. Any actions required for assessing or maintaining study-subject safety will continue as required, despite termination of the study by the Sponsor.

Details for study termination due to AESC are provided in Section 7.8.2.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria for All Cohorts

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

- Able to provide written informed consent
- Adult subjects ≥ 18 years
- Disease measurable by RECIST 1.1 criteria using either CT or MRI scan
- ECOG performance status of 0 or 1
- All subjects must have adequate archival tumor sample (slides or archival FFPE block[s] containing tumor that has not been previously irradiated; FFPE blocks are preferred to slides, and newly obtained biopsies are preferred to archived tissue. Refer to the laboratory manual for further instructions). Excepted are subjects who consent to having a fresh tumor biopsy to provide a fresh tumor sample instead of the archival tumor sample.
- Female subjects of childbearing potential must agree to use a highly effective method of birth control during and for 4 weeks after completion of study. Women are considered to be of childbearing potential unless it is documented that they are over the age of 60 OR postmenopausal by history with no menses for 1 year and confirmed by FSH (using local reference ranges) OR have a history of hysterectomy and/or bilateral oophorectomy OR have a history of bilateral tubal ligation. Highly effective methods of birth control include combined hormonal birth control (oral, intravaginal, or transdermal), or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or intrauterine), intrauterine devices (IUDs), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (provided partner is the sole sexual partner and there has been a medical assessment of surgical success), or sexual abstinence as defined in Section 8.9.1.
- Fertile male subjects must be willing to practice a highly effective method of birth control for the duration of the study and continuing for 4 weeks after the last dose of XmAb18087 or pembrolizumab (when applicable). Highly effective methods of birth control include vasectomy or a condom in combination with double-barrier methods, spermicide, hormonal birth control, or IUD (nonhormonal) used by the woman.
- Able and willing to complete the entire study according to the study schedule

8.2. Additional Inclusion Criteria for Part A and Part B Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Parts A and B safety run-in and expansion cohorts:

- Histologically or cytologically confirmed metastatic MCC or locoregional MCC that has recurred following standard locoregional therapy with surgery and/or radiation therapy.

8.3. Additional Inclusion Criteria for Part A Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Part A safety run-in and expansion cohorts:

- Subjects must have progressed on or been ineligible for treatment with anti-PD1 or anti-PDL1 therapy.

8.4. Additional Inclusion Criteria for Part B Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Part B safety run-in and expansion cohorts:

- Subjects must be eligible to receive pembrolizumab as standard of care.

8.5. Additional Inclusion Criteria for Part C Cohorts:

In addition to the inclusion criteria above, the following criteria are required for Part C safety run-in and expansion cohorts:

- Histologically or cytologically confirmed extensive-stage SCLC that has progressed following standard therapies

8.6. Exclusion Criteria for All Cohorts

Subjects who meet any of the following criteria will be excluded from the study:

- History of prior organ or bone marrow transplant
- History of chronic lymphocytic leukemia
- Subjects currently receiving anticancer therapies
- Subjects who have received anticancer therapies within 2 weeks of the start of study drug (including chemotherapy, radiation therapy, immunotherapy, etc.)
- Prior therapy with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA4, OX40, CD137) AND were permanently discontinued from that treatment due to an IRAE
- Failure to recover from any IRAE from prior cancer therapy to ≤ Grade 1 (participants with ≤ Grade 2 neuropathy or endocrinopathies controlled by hormone replacement are eligible)
- Failure to recover from any other toxicity (other than immune-related toxicity) from previous anticancer treatment to ≤ Grade 2
- Known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 28 days prior to trial treatment.

- Have a history of (noninfectious) pneumonitis that required steroids or have current pneumonitis (history of radiographically visible but asymptomatic radiation pneumonitis is allowed)
- Platelet count $< 50 \times 10^9$/L
- Absolute neutrophil count $< 1.0 \times 10^9$/L
- AST $\geq 3 \times$ upper limit of normal (ULN), or if subject has known liver metastases, AST $\geq 7 \times$ ULN
- ALT $\geq 3 \times$ ULN, or if subject has known liver metastases, ALT $\geq 7 \times$ ULN
- Estimated creatinine clearance < 50 mL/min calculated by the Cockcroft Gault or Modification of Diet in Renal Disease formulas at screening
- Treatment with immunosuppressive therapy within 28 days of first dose of study drug
- History or evidence of any other clinically unstable/uncontrolled disorder, condition, or disease (including, but not limited to, cardiopulmonary, renal, metabolic, hematologic, or psychiatric) other than their primary malignancy that in the opinion of the Investigator would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
- Treatment for any serious bacterial, viral, parasitic, or systemic fungal infections within the 30 days prior to study entry
- Active known or suspected COVID-19 disease
- Active known or suspected autoimmune disease (except that subjects are permitted to enroll if they have vitiligo; type 1 diabetes mellitus; residual hypothyroidism due to an autoimmune condition that is treatable with hormone replacement therapy only; psoriasis, atopic dermatitis, or another autoimmune skin condition that is managed without systemic therapy; or arthritis that is managed without systemic therapy beyond oral acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDS])
- Positive test for HIV or hepatitis C antibodies
- Positive test for HBsAg or HBcAb (a subject whose HBsAg is negative and HBcAb is positive may be enrolled if an HBV DNA test is negative and either the subject is treated with potent antiviral therapy or is retested for HBsAg and HBV DNA every month)
- Subject is pregnant or breastfeeding, planning to become pregnant, or expecting to conceive or father children while enrolled in the study, up to the end of study (EOS) visit.
- Positive serum pregnancy test (ie, urine human chorionic gonadotropin) at screening

8.7. Additional Exclusion Criteria for Part B Cohorts: XmAb18087 in Combination with Pembrolizumab

In addition to the exclusion criteria in Section 8.6, subjects will be excluded from Part B safety run-in and expansion cohorts administered XmAb18087 in combination with pembrolizumab if they meet the following criteria:

- Prior treatment with therapeutics directed at anti-programmed cell death 1 (anti-PD1) or anti-programmed cell death ligand 1 (anti-PDL1)
- Have severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients

8.8. Withdrawal of Subjects

Subjects must be withdrawn if the β-HCG pregnancy test is consistent with pregnancy. Before permanent discontinuation, the treatment may be interrupted to confirm the positive pregnancy test. Pregnancy should be reported as described in Section 11.1.4.2.

The Principal Investigator (PI) also has the right to withdraw subjects from the study at his/her discretion for any of the following reasons:

- Disease progression
- Occurrence of an unacceptable serious or non-serious AE
- Failure to return for follow-up
- Uncontrolled intercurrent illness unrelated to the disease under study that renders continuing treatment with XmAb18087 unsafe or regular study visits impossible
- Investigator decision
- Subject decision
- Death
- Administrative reasons

Subjects will be considered to have completed/ended participation in the study at the time that a subsequent anticancer therapy is administered.

Whenever possible, the Sponsor must be notified within 24 hours if a subject is withdrawn from the study. The reason(s) for a subject's discontinuation from the study are to be recorded in the source documents and the subject's electronic case report form (eCRF).

The EOT eCRF must be completed for all subjects who discontinue XmAb18087 permanently.

For subjects who discontinue prematurely, all assessments described for the EOT visit should be performed at the scheduled visit date, if at all possible. If this is not possible, all assessments should be performed as close to the scheduled dates as is practicable. Post-treatment evaluations should be completed no later than 4 weeks after the final administration of XmAb18087 and prior to initiation of a new treatment for malignancy.

Subjects who are withdrawn for any reason may not reenter this study. The Study Sponsor, Xencor, reserves the right to terminate this clinical study at any time and for any reason.

8.9. Other Subject Restrictions

8.9.1. Avoidance of Pregnancy

Women are considered to be of childbearing potential unless there is a documented reason (ie, postmenopausal by history with no menses for 1 year and confirmed by FSH [using local reference ranges], OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy).

Women of childbearing potential must have a negative pregnancy test during screening and at Day 1 prior to study drug infusion and must use 1 highly effective method of birth control during the study and for 4 weeks following last dose of XmAb18087 or pembrolizumab (when applicable). Highly effective methods of birth control include combined hormonal birth control (oral, intravaginal, or transdermal), or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or intrauterine), IUDs, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (provided partner is the sole sexual partner and there has been a medical assessment of surgical success), or sexual abstinence. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Total abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. The Investigator is responsible for evaluating the reliability of the subject's ability to maintain sexual abstinence throughout the duration of the clinical trial.

Fertile male subjects must be willing to practice a highly effective method of birth control for the duration of the study and continuing for 4 weeks after the last dose of XmAb18087 or pembrolizumab (when applicable). Highly effective methods of birth control include vasectomy or a condom in combination with double-barrier methods, spermicide, hormonal birth control, or IUD (nonhormonal) used by the woman.

8.9.2. Use in Nursing Women

It is unknown whether XmAb18087 or pembrolizumab are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

9. TREATMENT OF SUBJECTS

9.1. Identity of Study Treatments

XmAb18087 is a humanized bsAb that binds both CD3 and the tumor antigen SSTR2 to recruit cytotoxic T cells that will kill SSTR2$^+$ tumor cells. Intravenous Stabilization Solution is a concentrated form of the XmAb18087 buffer that minimizes protein binding to the administration equipment.

XmAb18087 drug product is a sterile liquid supplied in single-use glass vials. [redacted]

Prior to dilution, the vial containing parenteral drug product should be inspected visually. If particulate matter and/or discoloration are noted, drug should not be administered, and the Sponsor should be notified.

Pembrolizumab (Keytruda®) is an approved humanized mAb targeting the cell surface antigen PD1. It will be administered at the dose and schedule of 400 mg IV over 30 minutes every 6 weeks. It is supplied as a 100 mg per 4 mL (25 mg/mL) solution in a single-dose vial. Pembrolizumab is provided by sites as standard of care for advanced MCC.

9.2. Concomitant Therapy

All medications (including over-the-counter medications and herbals) and blood products that are administered within the 30 days prior to start of study treatment and throughout a subject's participation in the study until the post-treatment follow-up visit must be recorded in the source document and on the eCRF. Concomitant medications for other medical conditions are permitted as clinically indicated, subject to the specific requirements outlined in Section 7.9.1 and 7.9.2.

9.2.1. Permitted Medications

Subjects who experience CRS should receive aggressive intervention and supportive measures as indicated. These may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, acetaminophen, and tocilizumab (see Section 11.3.3 or Appendix C for suggested management of infusion reactions, CRS, and neurologic toxicities).

Subjects who experience IRAE after pembrolizumab exposure should receive specific therapy in accordance with the guidelines in Table 18 and/or the NCCN guidelines for management of IRAEs (Appendix E)

In addition to required prophylactic medications, subjects may also receive the following additional therapy during the clinical trial:

- Antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, antihyperglycemics, and other medications intended to treat symptoms related to cancer, cancer therapy, or concurrent conditions. Other antitumor treatments may not be received.
- Antiviral treatments for subjects with a positive HBcAb (and negative HBV DNA test) at screening
- Transfusions of blood products such as red blood cells (RBCs) and platelets, if medically indicated
- Histamine receptor type 2 antagonists, or proton-pump inhibitors for treatment of indigestion, nausea, and/or vomiting
- Multivitamins, provided they be documented on the concomitant medications eCRF. No other vitamins or supplements will be permitted during this study without prior notification and approval of the Medical Monitor.

9.2.2. Excluded Medications

Subjects may not concurrently receive other therapeutics for treatment of their malignancy. It is suggested that subjects not receive live prophylactic vaccinations while enrolled in the study.

9.3. Subject Compliance

The Sponsor or its designee will monitor the study according to GCP guidelines. All investigational therapy will be prepared and administered at the study site, and complete records of administration doses, times, durations, and supportive therapies will be kept.

Dosing will be performed by trained, qualified personnel designated by the PI. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

9.4. Blinding and Randomization of Study Treatment

No randomization or blinding is required for this open-label trial.

9.5. Procedure for Breaking the Randomization Code

Not applicable.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. XmAb18087

As of 27 April 2020, XmAb18087 has been given to 42 human subjects; hence, the safety profile associated with this agent is not well known and caution should be exercised as infusion reactions, CRS, allergic reactions, or other unexpected reactions may occur.

10.1.1. Pretreatment of XmAb18087

Because administration of XmAb18087 has been associated with nausea and vomiting and has also been associated with symptoms of infusion reaction/CRS in subjects and a severe CRS reaction in 1 subject, prophylactic medications are to be administered to all subjects before at least the first [redacted].

10.1.2. Prophylaxis of Nausea and Vomiting

The following antiemetic and antinausea prophylactic medications are to be administered to all subjects before at least the first [redacted]

[redacted]

If a subject experiences nausea and/or vomiting despite prophylaxis, [redacted] are recommended for treatment of the symptoms.

Sites may also choose to use other or additional antinausea/vomiting medications for prophylaxis or treatment of symptoms, according to their practice and assessment of the subject's responses.

10.1.3. Prophylaxis of Infusion Reactions/Cytokine Release Syndrome:

It is also required that all subjects receive the following medications before at least the first 4 doses the of study drug:

a. Acetaminophen (Tylenol®): 650 mg PO once before dosing with XmAb18087
b. Diphenhydramine (Benadryl®): 50 mg PO once before dosing with XmAb18087
c. 10 to 20 mg IV dexamethasone (Decadron®) before dosing with XmAb18087

If a subject receives 4 consecutive doses of XmAb18087 without ≥ Grade 1 infusion reaction or CRS, the prophylaxis described above may be modified, including elimination and/or reduced doses of some required medications.

For guidelines on the treatment of infusion reactions and CRS, see Section 11.2 or Appendix C of this protocol.

If at all possible, infusions of XmAb18087 should start before 2 PM local time. This is especially important for the C1D1 and any first dose at an escalated level to ensure that adequate staffing and services are available to manage a severe episode of CRS. In addition, either a Principal

Investigator or subinvestigator (MD) must be readily available during, and for a minimum of 24 hours after, administration of an XmAb18087 dose.

10.1.4. Administration of XmAb18087

XmAb18087 administration should begin as soon as possible after the dosing solution is made. If there is a delay in administration, it [redacted] The full-calculated dose will be administered based on the subject's actual baseline weight measurement in kilograms. Following the first dose, subsequent doses will only be modified if the subject's weight changes by more than 10% from the Day -1 weight at which point it will be recalculated using the current weight.

XmAb18087 should not be administered as an IV push or bolus.

Study drug will be administered as an open-label solution at a constant rate [redacted] period. Precautions for CRS or infusion reactions or anaphylaxis should be observed during XmAb18087 administration. Due to the possibility that CRS, allergic reactions, or infusion reactions may occur, emergency resuscitation equipment (a "crash cart") and medications including steroids and tocilizumab should be present in the immediate area where subjects are receiving their infusions. Additional supportive measures should be available and may include, but are not limited to: acetaminophen, antihistamines, corticosteroids, IV fluids, bronchodilators, epinephrine, vasopressors, oxygen, and tocilizumab. Please refer to Section 11.3 or Appendix C for management of infusion reactions, CRS, and neurologic toxicities.

Vital signs will be measured and recorded as follows: immediately (within 60 minutes) prior to the infusion; during the infusion at 15, 30, and 60 minutes (± 5 minutes for each time point) from start time of the infusion; immediately (within 5 minutes) before EOI; and at 15, 30, and 60 minutes (± 5 minutes for each time point), then hourly (± 5 minutes) for a 3-hour period, after EOI. Oxygen saturation levels will be captured with each vital sign collection; however, pulse oximetry monitoring must be maintained continuously throughout the entire admission or observation period for each administration of XmAb18087. All supportive measures consistent with optimal subject care will be provided throughout the study according to institution standards. For subjects who a) tolerate 3 consecutive infusions without an infusion reaction during the observation period and b) have completed 4 infusions at the highest dose for that subject, the postinfusion observation period and vital signs assessment may be reduced from 4 hours to 2 hours.

10.2. Pembrolizumab (Keytruda®)

Pembrolizumab is an FDA-approved humanized monoclonal antibody that blocks the interaction between PD1 and its ligands, PDL1 and PDL2.

10.2.1. Administration of Pembrolizumab

In dosing cohorts incorporating pembrolizumab (Part B only), pembrolizumab will be administered by IV infusion on Days 15 and 36 of each 42-day cycle. Pembrolizumab will be provided by sites as standard of care for advanced MCC.

Vital signs associated with the pembrolizumab infusion will be measured and recorded as follows: immediately prior (within 10 minutes before blood sampling) to the start of the infusion; during the infusion at 5 and 15 minutes (± 2 minutes) from the start time of the infusion; immediately (within 2 minutes) before the EOI; and at 15 minutes (± 2 minutes) after EOI. During Cycle 1, the subject will be observed for 4 hours after the infusion. On subsequent pembrolizumab administration days, the subject may be discharged 15 minutes postinfusion, if stable.

Pembrolizumab will be administered at a dose of 400 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between −5 minutes and +15 minutes is permitted (ie, infusion time is 30 minutes [−5 minutes/+15 minutes]). For additional information, refer to the pharmacy manual and the pembrolizumab prescribing information (Keytruda® Package Insert, 2020).

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

10.2.2. Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 2000 mg or ≥ 5 × the indicated dose.

No specific information is available on the treatment of overdose of XmAb18087, or of pembrolizumab. In the event of overdose of either drug, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

10.3. Safety Criteria for Dose Adjustment or Stopping Dose

10.3.1. Criteria for Adjustment or Stopping Dose of XmAb18087

Subjects experiencing a significant toxicity should be treated with standard medical interventions (eg, acetaminophen for fever) as appropriate.

For guidelines on management of infusion reactions/CRS/neurologic toxicity, and rules regarding study drug adjustment/discontinuation after an infusion reaction/CRS/neurologic toxicity, see Section 11.3.3 or Appendix C.

Subjects experiencing an AE that meets AESC criteria (as defined in Section 7.8 above) will have subsequent dosing held until recovery to baseline or ≤ Grade 2 following the AE. In the event that a > Grade 2 drug-related toxicity persists > 14 days and/or 2 consecutive doses are missed, the subject will be permanently discontinued from the study drug treatment. Subjects who experience the same AE that meets AESC criteria on 2 consecutive infusions will be subsequently treated at one dose level lower than the dose at which the AE occurred. Rechallenge with study drug is not permitted for any Grade 4 toxicity.

10.3.2. Criteria for Adjustment or Stopping Dose of Pembrolizumab

Refer to Table 18 for dose modification and management guidelines for IRAEs related to pembrolizumab. Additional guidelines from the NCCN on the diagnosis and management of IRAEs can be found in Appendix E. Rechallenge with pembrolizumab is not permitted for the following:

- Any IRAE that requires permanent discontinuation of study drug according to the guidelines in Table 18.
- Any severe (Grade 3) or life-threatening (Grade 4) infusion-related reaction.

If it is determined that pembrolizumab must be permanently discontinued based on the above criteria, dosing with XmAb18087 must also be discontinued.

10.4. Study Treatment Packaging and Labelling

10.4.1. Packaging and Labelling of XmAb18087

XmAb18087 and the IV Solution Stabilizer will be supplied in single-use glass vials.

XmAb18087 and the IV Solution Stabilizer will be supplied by Almac. IMPs will be packaged and labeled according to applicable local and regulatory requirements.

10.4.2. Storage of XmAb18087

Vials containing XmAb18087 and IV Solution Stabilizer must be stored under refrigeration at [redacted] in an appropriately secured area accessible only to the pharmacist, the PI, or a duly designated person. Since XmAb18087 does not contain preservatives, opened vials of XmAb18087 must be used within 24 hours.

10.4.3. Preparation of XmAb18087

Note that XmAb18087 has PD effects in vivo at very low concentrations and therefore each product vial must be highly diluted before administration.

Prior to administration, XmAb18087 will be diluted to the required final concentration in 1 or more ethylene/polypropylene copolymer infusion bags [redacted]. Prior to dilution, the vial containing parenteral drug product should be inspected visually. If particulate matter and/or discoloration are noted, drug should not be administered, and the Sponsor should be notified. After dilution, the bag containing XmAb18087 should be gently inverted 2 to 3 times to mix the solution. **THE BAG MUST NOT BE SHAKEN**; excess agitation may cause aggregate formation. See the XmAb18087 Pharmacy Manual for additional details.

10.4.4. Packaging and Labeling of Pembrolizumab

Pembrolizumab will be obtained from commercial sources and administered to subjects in the combination therapy cohorts on Day 15 of each 42-day cycle as directed by the package insert (Keytruda® Package Insert, 2020).

10.4.5. Storage of Pembrolizumab

Store under refrigeration at 2 °C to 8 °C, do not freeze, do not shake, and protect from light, as per the pembrolizumab prescribing information (Keytruda® Package Insert, 2020).

10.5. Study Treatment Accountability, Handling, and Disposal

Detailed instructions and procedures for study-drug dispensing are included in the Pharmacy Manual.

Accurate accounting of all study drug must be maintained. The PI agrees to keep an inventory of study drugs using local investigational pharmacy drug accountability logs. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

These records shall include dates, quantities, batch numbers, expiry dates, and the unique code numbers assigned to the study drug and to the study subjects.

The Investigator shall be responsible for ensuring records adequately document that the subjects were provided the doses specified in the protocol and that all study drug received from the Sponsor is reconciled.

Upon completion or termination of the study, any used or partially used vials, unused study medication, diluted drug dosing solutions, or IV Solution Stabilizer should be destroyed in compliance with local investigational pharmacy policies or returned to the Sponsor or its designee.

11. ASSESSMENT OF SAFETY

Adverse event reporting will begin with the signing of the informed consent document (Screening) and will continue until the end of the subject's participation in the study: ie, until a subject has discontinued or completed the study.

Safety and tolerability assessments will include the following:

- AEs
- Vital signs
- PE findings
- Clinical laboratory safety assessments
- ECG parameters

Biomarkers of CRS (IL-2, IL-6, IL-8, IL-10, IFN-γ, IL-13, IL-1B, and TNF-α) will also be collected as additional safety information.

Details for management of hypersensitivity reactions, CRS, and neurologic toxicities are provided in Section 11.3.2, 11.3.3.3, and 11.3.3.4, respectively, as well as in Section 11.3.3 and Appendix C of this protocol.

11.1. Adverse Events

11.1.1. Definitions

11.1.1.1.1. Adverse Event

An AE is any untoward medical occurrence in a study-subject administered IMP. The AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Adverse events may include the onset of new illness and the exacerbation of preexisting conditions.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, eg, those occurring during treatment-free periods (including Screening or post-treatment follow-up periods), in association with study-related procedures and assessments, or under placebo. For IMPs, lack of efficacy may be an expected potential outcome and should not be reported as an AE, unless the event is unusual in some way, eg, greater in severity.

Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Preexisting conditions will be recorded as part of the subject's medical history.

11.1.1.1.2. Serious Adverse Event

AEs are classified as "serious" and "non-serious" for regulatory reporting purposes. The classification determines the procedures used to document and report the AE.

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the investigational product or comparator, that fulfills one or more of the following:

- Results in death
- Is life-threatening; this means that the subject was at immediate risk of death at the time of the event. It does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation in existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is an important medical event. Important medical events are events that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the patient and may require intervention to prevent one of the other serious outcomes listed above.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in subject hospitalization, and the development of drug dependency or drug abuse. Hospitalizations for planned surgical/medical elective procedures will not be reported as SAEs. In addition, hospitalizations of ≤ 24 hours will not be reported as SAEs. A death due to disease progress will not be considered an expedited report.

The following will **not** be reported as an SAE:

- Hospitalization for planned surgical/medical elective procedures per protocol for study drug administration, any admission required for disease assessments, or any admissions planned prior to enrollment (eg, planned surgical/medical elective procedures) will not be recorded/reported as an SAE.
- Hospitalization or death due to disease progression. Signs/symptoms and conditions related to disease progression of the primary condition under the investigation (eg, tumor-related pain, metastasis, new lesions, etc).

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring hospitalization for monitoring purposes would be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

11.1.1.1.3. Abnormal Laboratory Values

Clinically significant abnormal laboratory results which are not caused by the underlying disease or are not consistent with the subject's medications will be recorded as AEs and the relationship

to the study drug will be indicated as below. Laboratory values outside the normal range will be assigned one of the following categories by the Investigator or designee:

1. Not clinically significant, minor out of range value or finding. AE - No
2. Not clinically significant, out of range value or finding explainable by anticipated or known effect of study drug or concomitant drugs. AE - No
3. Clinically significant but consistent with the subject's underlying disease. AE - No
4. Clinically significant out of range value or finding. AE – Yes

In general, a clinically significant laboratory value or finding would require some diagnostic or therapeutic intervention other than repeating the test.

11.1.2. Recording of Adverse Events

AEs should be collected and recorded for each subject from the date the ICF was signed until the end of their participation in the study, ie, the subject has discontinued or completed the study. All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Sponsor medical representative, until there is a satisfactory explanation for the changes observed, or until the subject is lost to follow-up.

Any new SAEs that are suspected to be related to study drug occurring up to 28 days after the last administration of study drug should be reported to ICON according to Section 11.1.5. Adverse events may be volunteered spontaneously by the study subject, discovered by the study staff during physical examinations, or by asking an open, nonleading question such as "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken with the study drug because of the AE will be documented together with the Investigator's assessment of the seriousness on the AE and causal relationship to study drug and/or study procedure.

All AEs should be recorded individually unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom. The date (and time, if known) that the Investigator or study site is first made aware of the AE (or any subsequent follow-up information is received) will be documented. The AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Each AE will be assessed by the Investigator with regard to the categories discussed in the sections below.

11.1.2.1. Intensity

The Investigator will assess all AEs for severity utilizing the NCI-CTCAE grading scale (Version 5.0). AEs not contained within CTCAE Version 5.0 will be rated on a five-point scale (Table 8):

Table 8: Severity Grading Scale

Mild (Grade 1)	Mild events are those which are easily tolerated with no disruption of normal daily activity.
Moderate (Grade 2)	Moderate events are those which cause sufficient discomfort to interfere with daily activity.
Severe (Grade 3)	Severe events are those which incapacitate and prevent usual activity.
Life-threatening (Grade 4)	An adverse event that has life-threatening consequences, for which urgent intervention is indicated, that puts the subject at risk of death at the time of the event if immediate intervention is not undertaken, or that causes blindness or deafness.
Fatal (Grade 5)	The termination of life as a result of an adverse event.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

11.1.2.2. Causality

The Investigator will assess the causality/relationship between the IMP and the AE. One of the following categories should be selected based on good medical and scientific judgment, considering the definitions in Table 9 and all contributing factors.

Table 9: Causality Grading Scale

Related	A clinical event, including laboratory test abnormality that occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Probably Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possibly Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely Related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
Not Related	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

AE = adverse event.

[a] Dechallenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge is when a drug suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

11.1.2.3. Action Taken with Study Treatment

Action taken with XmAb18087 (and pembrolizumab, when applicable) will be reported as one of the following:

- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable

11.1.2.4. Outcome

Outcome will be defined as follows:

- Death related to adverse event
- Not recovered or not resolved

- Recovered or resolved
- Recovered or resolved with sequelae
- Recovering or resolving
- Unknown

11.1.3. Preidentified Immune-Mediated Adverse Events

See the pembrolizumab package insert (Keytruda® Package Insert, 2020) for a description of potential IRAEs. Guidelines for the management of IRAEs can be found in Table 18 and Appendix E.

11.1.4. Adverse Events of Special Interest

IRAEs (Part B only) and infusion reactions (hypersensitivity reactions and CRS) are designated events of special interest in this protocol. Refer to Section 11.3.

11.1.4.1. Deaths

Should a death occur within the study period or within 28 days after the last administration of study drug (or until the subject initiates other anticancer therapy, whichever comes first), an AE form and an SAE form should be completed, detailing the AE that resulted in the death (death is an outcome, not an event). The SAE must be reported to the Medical Monitor within 24 hours. The report should contain a comment regarding the coinvolvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

11.1.4.2. Pregnancy

The teratogenic potential of XmAb18087 is unknown. Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman; however, there are no available human data informing the risk of embryo-fetal toxicity (Keytruda® Package Insert, 2020). The Investigator and Sponsor have a responsibility to monitor the outcome of all pregnancies, including pregnancies in female partners of male participants, reported during the clinical study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. All notifications of pregnancy should be documented and reported through 120 days following cessation of study treatment (or through 30 days following cessation of study treatment if the subject initiates new anticancer therapy), whether or not there is an associated AE or SAE.

Each pregnancy notification must be reported by the Investigator to the Sponsor and ICON within 24 hours after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the clinical study or if the clinical study has finished. The follow-up period will be deemed to have ended when the health status of the child has been determined on its birth.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor and ICON on the pregnancy outcome report form within 24 hours after he/she has gained knowledge of the normal delivery or elective abortion, or other outcome.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours of awareness in accordance with the procedure for reporting SAEs.

11.1.5. Reporting Serious Adverse Events

The Investigator will review each potential SAE and evaluate the intensity and the causal relationship of the event to IMP. All potential SAEs will be recorded from signing of informed consent until the end of the subject's participation in the study: ie, the subject has discontinued or completed the study, except for the long-term follow-up period. During the long-term follow-up period, only SAEs that come to the attention of the Investigator and that the Investigator believes to have a reasonable causal relationship to the IMP will be reported.

The Investigator is responsible for reporting SAEs related to pembrolizumab to regulatory authorities per reporting guidelines.

The Investigator is responsible for providing notification to ICON of any potential SAE, whether deemed IMP-related or not, that a subject experiences during his/her participation in study within 24 hours of becoming aware of the event. ICON will provide the information to the Sponsor.

The initial SAE form should be completed and emailed to [redacted] with the following information:

- Study number
- Subject number
- Gender
- Year of birth
- Name of PI and full clinical site address
- Name of the reporter
- SAE event term
- Details of SAE
- Criterion for classification as "serious"
- Study drug name, dose, and treatment start date
- Date of SAE onset
- Date of SAE first awareness (by Investigator or study site staff)
- Causality assessment

ICON will request clarification of omitted or discrepant information from the initial notification. The Investigator or an authorized delegate is responsible for providing the requested information to ICON within 24 hours of the request.

Initial reports of SAEs must be followed up as soon as possible with detailed descriptions; this may include clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc.) with the study subject's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and forwarded to ICON within 24 hours of receipt of the information.

If a new SAE report form for the same SAE is completed, then the Investigator must sign and date the SAE form and mark the form as "follow-up." ICON and/or the Sponsor may also request additional information on the SAE in order to obtain the full clinical picture, to which the PI or an authorized delegate must respond to ICON within 24 hours of the request.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

[redacted] (Americas)

[redacted] (Europe)

Emergency contact number: [redacted] (within US)

[redacted] (toll number and outside of US)

1. E-mail your SAE form to the study specific e-mail address above.

2. Provide ICON with the name of the PI, your name, the telephone number where you can be reached and the protocol number and title.

3. Immediately forward the SAE form and any supporting documentation to ICON; this must be done within 24 hours of becoming aware of the event.

11.1.6. Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Sponsor medical representative, until there is a satisfactory explanation for the changes observed, or until the subject is lost to follow-up.

11.1.7. Treatment/Reporting of Overdose

In the event of an overdose, the physician should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Obtain a plasma PK sample if requested by the Medical Monitor (determined on a case-by-case basis)
- Document the quantity and duration of the excess dose

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

All overdose cases should be reported as SAEs.

11.2. Investigational New Drug Safety Reports

During the course of the study, the Sponsor may determine that certain safety reports are required to comply with regulations. The PI may receive a letter called an "Investigational New Drug (IND) Safety Report." These reports must be submitted to the IRB per local requirements as soon as possible, and documentation of this submission should be available to the Sponsor or ICON.

11.3. Guidelines for Prophylaxis and Management of Hypersensitivity Reactions, Cytokine Release Syndrome, and Neurological Toxicity Attributed to XmAb18087

Because administration of XmAb18087 has been associated with symptoms of infusion reaction/CRS in some subjects, it is required that all subjects receive the following medications before at least the first 4 doses of XmAb18087:

a. Acetaminophen (Tylenol®): 650 mg PO once before dosing with XmAb18087
b. Diphenhydramine (Benadryl®): 50 mg PO once before dosing with XmAb18087
c. 10 to 20 mg IV dexamethasone (Decadron®) before dosing with XmAb18087

If a subject receives 4 consecutive doses of XmAb18087 without ≥ Grade 1 infusion reaction/CRS, the prophylaxis described above may be modified, prophylactic medications are to be administered to all subjects before at least the first 4 doses of the study drug.

11.3.1. Introduction and Grading

Grading of toxicity, including allergic/hypersensitivity reactions, is by CTCAE version 5.0, except for CRS, which is graded using the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading (Lee, 2019) See Table 10 for these definitions.

All sites should review and implement the general guidelines for the use of tocilizumab and IV fluids discussed below in Sections 11.3.3.1 and 11.3.3.2. Otherwise, management of CRS and other infusion-related reactions should be per standard investigational site procedures. Or, if there are no local standards or if they are incomplete, the approaches discussed here may be used.

The Xencor Medical Monitor ([redacted]) should be contacted immediately by email or phone if questions arise concerning the grade of an infusion reaction. [redacted] email is [redacted], and his telephone number is [redacted].

Table 10: American Society for Transplantation and Cellular Therapy Cytokine Release Syndrome Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[b]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.
Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading.
[a] Fever is defined as temperature ≥ 38 °C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5 °C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

11.3.2. Cytokine Release Syndrome Versus Allergic or Hypersensitivity Reactions

Cytokine release syndrome is mechanistically different from allergic/hypersensitive reactions (Lee, 2019), although some of the manifestations are common to both AEs and both have been reported to occur with therapeutic antibodies. An acute infusion reaction is often caused by a type 1 hypersensitivity mechanism due to immunoglobulin-E (IgE)-mediated release of histamines and prostaglandins, although a direct interaction with mast cells and basophils can also occur. It is less clear how cytokine release is triggered, although it is likely to be associated with immune cell activation; in this case, there is evidence that immunologic cascade is initiated by triggering of CD3-expressing T lymphocytes, resulting in TNF-α mediated monocyte/macrophage activation and systemic toxic cytokine release (Li, 2019).

Signs and symptoms usually develop during or shortly after drug infusion in hypersensitivity reactions, are more likely to occur after several doses of the drug and are largely related to histamine release. Typical signs and symptoms of hypersensitivity reaction include rash/urticaria, flushing, pruritus, fever, dyspnea, cough, and hypotension, although the following may also occur (Lenz, 2007):

- Arthralgia

- Bronchospasm
- Confusion, mental status changes, and/or delirium
- Dizziness
- Fatigue (asthenia, lethargy, malaise)
- Hallucinations
- Headache
- Hypertension
- Myalgia
- Nausea and/or vomiting
- Rigors/chills
- Diaphoresis
- Tachycardia

Cytokine release syndrome, on the other hand, is more likely to occur after the first dose or first escalated dose of drug than after subsequent doses. It may begin somewhat later and is more likely to be associated with hepatic and neurologic complications, including the following:

- Any of the hypersensitivity signs or symptoms listed above
- Aphasia or word-finding difficulty
- Elevated d-dimer and/or hypofibrinogenemia
- Fatigue (asthenia, lethargy, malaise)
- Gait disturbance/dysmetria
- Hallucinations
- Seizures
- Transaminitis and/or hyperbilirubinemia
- Tremor

The Xencor Medical Monitor should be contacted immediately if questions arise concerning the grade and/or treatment of the infusion reaction.

11.3.3. Treatment Guidelines for Cytokine Release Syndrome

11.3.3.1. Use of Tocilizumab for Cytokine Release Syndrome

Tocilizumab is a therapeutic antibody that interferes with binding of IL-6 to the IL-6 receptor. It has been used to decrease the severity and possibly mortality of severe CRS (Frey, 2017), and early administration may be useful in improving outcomes. Below are suggested guidelines for its use:

- Sufficient tocilizumab (dose of 8 mg/kg) should be readily available to the area where subjects are receiving their infusions and being observed post infusion.
- Prompt tocilizumab therapy should be strongly considered if:
  - Oxygen saturation falls below 90% on room air, **OR**
  - Systolic blood pressure falls 20 mm Hg below predose measurements and below 100 mm Hg, **OR**
  - Temperature of > 38 °C (100.4 °F) in the presence of new or worsening dyspnea and/or tachypnea and/or rigors and/or tachycardia (heart rate [HR] > 110 bpm), **OR**
  - Early discovery of hepatic transaminase elevation. (Note that peak transaminase elevation appears to occur within 24 hours, so that it is unlikely that tocilizumab treatment on the day after study drug administration would affect the course or outcome in the absence of concurrent symptoms or signs of CRS).
- Repeat dosing of tocilizumab may be necessary if signs and symptoms persist or return after initial treatment.

11.3.3.2. Fluid Management

Cytokine release syndrome is sometimes associated with myocardial dysfunction, pulmonary edema, or capillary leak syndrome (Shimabukuro-Vornhagen, 2018). Although there are little or no data regarding use of anti-CD3 antibodies and the need for fluid management, it seems prudent to monitor subjects for weight gain and limit IV fluid administration in the acute setting.

- If a subject is noted to have had a ≥ 10% increase in body weight over the previous 2 weeks in association with new or significantly increased bilateral lower extremity edema, dosing should be delayed until this finding is evaluated and, if indicated, treated.
- For acute hypotension, an IV fluid bolus should be limited to 500 mL of normal saline or the equivalent.
- If there is not an adequate response to fluids, treatment with tocilizumab (and vasopressors, if necessary) should be considered rather than additional fluid boluses.

11.3.3.3. Cytokine Release Syndrome Treatment Guidelines by Grade

The following are treatment guidelines for XmAb18087 treatment-related infusion reactions (Lee, 2019); since it can be difficult to differentiate between different infusion reaction etiologies, both are included here.

Grade 1:

- Administer acetaminophen and/or diphenhydramine or dexamethasone to treat signs and symptoms if clinically indicated.
- Vital signs should be measured every 15 minutes or less as clinically indicated.
- Obtain a blood sample for cytokine analysis during the event and approximately 4 hours later, unless to scheduled cytokine monitoring is already in progress.

- Monitor the subject for worsening of condition; if severity of event increases to a higher grade, stop the infusion, administer appropriate treatment, and refer to guidelines below for more severe infusion reactions.
- It may be useful to premedicate the subject with acetaminophen and antihistamines prior to the next infusion.

Grade 2:

- Hypotension responsive to fluids or a low dose of a single pressor, or mild respiratory symptoms treatable with low-flow oxygen are signs of Grade 2 toxicity. Older subjects or those with significant comorbidities may be at higher risk of decompensation in this situation.
- **Discontinue the infusion** and administer acetaminophen and/or diphenhydramine or dexamethasone to treat signs and symptoms if clinically indicated. Once symptoms have resolved, slow the infusion rate by 50% of the baseline rate. If after 1 hour, the subject's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes, as tolerated, to the baseline rate.
- Note that older subjects or those with significant comorbidities may be at higher risk of decompensation in this situation. When reactions occur in these vulnerable subjects, or in the case of rapidly escalating reactions, consider treatment with **tocilizumab** 4 to 8 mg/kg IV over 1 hour, with or without dexamethasone 10 to 20 mg IV (or equivalent).
- Vital signs should be measured every 15 minutes or less as clinically indicated. For subjects who are able to tolerate an increase in the infusion rate back to baseline and maintain normal blood pressure for 30 minutes after the rate increase then, at the discretion of the Investigator, the frequency of vital sign assessment may be reduced to every 30 minutes during the infusion.
- Obtain a blood sample for cytokine analysis during the event and approximately 4 hours later, in addition to scheduled cytokine monitoring if already in progress.
- Monitor the subject for worsening of condition; if severity of event increases to a higher grade, stop the infusion, administer appropriate treatment, and refer to guidelines below for Grades 3 and 4 infusion reactions.
- Subjects with maximum Grade 2 infusion reaction may continue on study and should receive prophylactic premedication with acetaminophen 650 mg PO and diphenhydramine hydrochloride 25 to 50 mg IV or PO prior to all subsequent XmAb18087 infusions.

Grade 3 and 4:

- **Stop the infusion** and disconnect the infusion tubing from the subject.
- Aggressive supportive care should be given immediately. Vasopressors, fluids, oxygen, epinephrine or bronchodilators, ventilatory support, antipyretics, and analgesics should be used as indicated.

- Treatment with tocilizumab 4 to 8 mg/kg IV over 1 hour with or without dexamethasone 10 mg IV (or equivalent) is strongly encouraged for CRS due to the high risk of progression and permanent organ dysfunction.
- Hospital admission for observations is almost always indicated, usually to an intensive care unit, since an initial appearance of improvement may quickly yield to rapid decompensation.
- Subjects with Grade 3 CRS or infusion reaction may be rechallenged once resolved. Subjects with recurrent Grade 3 or any Grade 4 infusion reaction should not receive further XmAb18087 treatment but will continue to be followed on the protocol (ie, for 4 weeks after last dose).
- Obtain a blood sample for cytokine analysis during the event and approximately 4 hours later, in addition to scheduled cytokine monitoring if already in progress.
- Obtain a sample for ADA testing as close to the onset of the event as possible, at the resolution of the event, and 28 days following the event.
- Notify the Xencor Safety Monitor or Xencor Medical Monitor, [redacted] (Telephone: [redacted]; Email: [redacted]), immediately.

11.3.3.4. Neurotoxicity

In addition to CRS, another toxicity observed after chimeric antigen receptor T cell (CAR-T) therapy and CD3 bispecific antibodies is neurotoxicity. Immune effector cell-associated neurotoxicity syndrome (ICANS) may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema (Lee, 2019). Neurotoxicity was previously considered in aggregate with CRS, but is now treated separately, due to its timing and response to treatment.

Neurologic symptoms may occur during or after CRS symptoms, but rarely precede CRS symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy. Headache is a nonspecific symptom, frequently occurring during fever or after chemotherapy in patients without other neurologic dysfunction. Thus, headache alone is not a useful marker of ICANS. Expressive aphasia, on the other hand, appears to be a very specific symptom of ICANS (Lee, 2019).

A consensus grading scheme, which is a slightly modified version of the CARTOX-10 screening tool, which incorporated key elements of the Mini-mental State Examination (MMSE), the Immune Effector Cell-Associated Encephalopathy (ICE) score, will be used for the grading of ICANS (Table 9). It is important to note that the 10-point ICE screening tool is helpful for assessing patients for encephalopathy; however, the grading of ICANS requires assessment of the 10-point ICE score as well as evaluation of other neurologic domains, such as level of consciousness, motor symptoms, seizures, and signs of elevated ICP/cerebral edema, which may occur with or without encephalopathy. The ASTCT ICANS toxicity grading system is shown in Table 10. This grading scale will be used to assess neurotoxicity, rather than the CTCAE 5.0.

Table 11: Immune Effector Cell-associated Encephalopathy Scoring

ICE
Orientation: orientation to year, month, city, hospital: 4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
Attention: ability to count backwards from 100 by 10: 1 point

ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy (score).
Scoring: 10, no impairment;
7 - 9, Grade 1 ICANS;
3 - 6, Grade 2 ICANS;
0 - 2, Grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS (Lee, 2019).

Table 12: American Society for Transplantation and Cellular Therapy Immune Effector Cell-associated Neurotoxicity Syndrome Consensus Toxicity Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7 - 9	3 - 6	0 – 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy (score); ICP = intracranial pressure; N/A = not applicable; VI = sixth.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

[a] A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0 (Lee, 2019).

It has been speculated that high levels of IL-6 may directly mediate neurotoxicity in this situation (Lee, 2014).

Clinical management of neurotoxicity consists of the following:

- Monitor subjects closely for signs and symptoms of these events (including administration of mental status and neurologic examinations when these seem clinically warranted).
- If neurotoxicity becomes evident, a blood sample for cytokine analysis should be drawn at that time, and again 4 hours later, in addition to scheduled cytokine monitoring if already in progress.
- If neurologic toxicity is Grade 4, discontinue XmAb18087, if still infusing.
- For Grade 3 neurologic toxicity, withhold both drugs until the toxicity has recovered to ≤ Grade 1 (mild) and has remained at ≤ Grade 1 for at least 3 days before restarting therapy. Restart XmAb18087 at 75% of the previous dose. Restart pembrolizumab at the full dose. Escalate back to full dose at the time of the next dose if ≥ Grade 2 toxicity does not recur. If ≥ Grade 2 toxicity reoccurs at 75% dose, or if < Grade 2 toxicity takes more than 7 days to resolve, discontinue permanently.
- For severe neurologic symptoms, administer additional dexamethasone 10 mg intravenously and repeat every 12 hours if symptoms do not abate rapidly, or treat according to the clinical site's institutional protocol for such reactions.
- For recurrent seizures, anticonvulsant therapy may be necessary.

11.4. Guidelines for Prophylaxis and Management of Infusion Reactions Attributed to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Refer to the pembrolizumab prescribing information (Keytruda® Package Insert, 2020) for diagnosis, management, prophylaxis, and dose modification for infusion-related reactions related to pembrolizumab administration.

11.5. Laboratory Assessments

Safety clinical laboratory assessments will be performed by ICON Central Labs. Specified predosing safety laboratory assessments will also be performed by clinical site local laboratories so that site personnel are able to review the results before administering XmAb18087. In addition, investigators may also perform locally any laboratory assessments that they feel are necessary to protect subject safety.

Blood samples should be taken using standard venipuncture techniques. Blood sampling will be performed according to site or laboratory standard operating procedures (SOPs).

Unless otherwise prescribed within this clinical protocol, assessments during Cycle 1 Days 1, 8, and 15 should be completed ± 1 hour of the scheduled time; for other days during Cycle 1 ± 3 hours; and for subsequent cycles and within ± 2 days of the scheduled day. Disease assessments by RECIST and by radionuclide imaging should be performed within ± 2 days of the scheduled day. Imaging will be collected and stored for potential central assessment at a later date. Details for laboratory assessments, PK, PD, flow cytometry, and biobanking are provided in the Laboratory Manual.

The following laboratory variables will be determined as outlined below:

Hematology: RBC, hemoglobin, erythrocyte mean corpuscular volume, RBC distribution width, white blood cell (WBC) with differential (percent and absolute; neutrophils, lymphocytes, monocytes, eosinophils, basophils, and nucleated RBCs), and platelet count.

Coagulation panel: prothrombin time/international normalized ratio and activated partial thromboplastin time.

Clinical chemistry: Chemistry panel (sodium, chloride, potassium, bicarbonate, blood urea nitrogen, creatinine, glucose, uric acid, calcium, phosphorous, total bilirubin, ALT, AST, total protein, albumin, alkaline phosphatase, and lactate dehydrogenase), serum gamma-glutamyl transpeptidase, amylase, and lipase.

Urinalysis: pH, specific gravity, ketones, leukocyte esterase, bilirubin, blood protein, RBCs, WBCs, hyaline casts, RBC casts, WBC casts, granular casts, waxy casts, broad casts, and fatty casts.

Pregnancy test: Serum β-hCG pregnancy test for women of childbearing potential or FSH for postmenopausal women.

11.6. Electrocardiogram Assessments

The timing of ECGs is noted in Table 7. On all dosing days in Cycle 1 and selected dosing days in cycles after Cycle 1, supine ECGs will be performed predose.

The 12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 minutes. The ECG will include all 12 standard leads. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QTc interval.

All ECGs must be evaluated by a qualified physician for the presence of abnormalities.

11.7. Physical Examination

Complete or abbreviated (symptom-directed) PEs will be performed as indicated in Table 7.

The complete PE includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

An abbreviated PE is symptom-directed and need not include detailed examination of all systems.

11.8. Vital Signs

Vital signs will be assessed at as indicated in Table 7. All vital signs should be taken with the subject in the same position. On nondosing days, vital signs should be measured prior to blood sampling. The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute [bpm])
- Respiratory rate (breaths per minute)

- Body temperature (°C)
- Supine BP and heart rate recordings will be made after the study subject has been recumbent and at rest ≥ 5 minutes
- Blood oxygen saturation by pulse oximetry. Oxygen saturation levels will be captured at each vital sign collection; however, pulse oximetry monitoring must be maintained continuously throughout the entire admission or observation period for each administration of XmAb18087.

12. ASSESSMENT OF EFFICACY

Radiographic tumor evaluation will be performed at baseline and at all other disease assessment time points per RECIST 1.1 criteria (Appendix A). If additional clarification or detail is needed, please consult the literature referenced or the Sponsor's Medical Monitor.

The timing for these evaluations will be uniform. Initial evaluation will occur within 14 days (60 days for NETSPOT® gallium 68 dotatate PET/CT) before administration of the first dose of XmAb18087, and follow-up evaluation will be performed on Cycle 1 Day 40 ± 2 days. Reevaluation will be performed after every cycle, as long as the subject continues on study, and at EOT. NETSPOT® gallium 68 dotatate PET/CT scan will be performed and interpreted locally. Copies of images and reports will be collected and sent to Xencor, Inc., for interpretation and archiving. Scans used for RECIST assessments will be performed and interpreted locally. Copies of these images will be collected and stored for potential central assessment at a later date.

13. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

13.1. Serum Sampling for Pharmacokinetic Analyses, Anti-drug Antibodies, Cytokines, and Inflammatory Factors

The Sponsor or designee will provide cryotubes, labels, and requisition forms. Serum cryotubes will be labeled at the clinical site with the subject number, date, visit day and time point, and time of sampling. Samples will be stored on site at -70 °C until the Sponsor notifies the sites to ship the samples on dry ice to the designated laboratory for sample analysis. Detailed instructions for processing and shipping serum samples are provided in the Laboratory Manual. Venous blood samples for serum analyses of PK, ADA, and the cytokine and inflammation panel will be obtained according to the Schedule of Assessments (Table 7).

13.2. Pharmacokinetics

Samples for PK analysis will be collected at the times specified in the Schedule of Assessments (Table 7). The exact time and date of the blood draw must be accurately recorded using an unambiguous format such as DD MON YYYY and HH:MM on a 24-hour clock. Missed samples will be considered protocol deviations.

13.3. Pharmacodynamics

Baseline and serial assessment of B-cell, NK-cell, and T-cell numbers and T-cell activation will be assessed in peripheral venous blood. The Sponsor/designated vendor will provide blood sampling tubes, label, requisition forms, and shipping containers. Samples for flow cytometry should be shipped immediately at ambient temperature. Detailed instructions for processing and shipping flow cytometry samples are provided in the Laboratory Manual. For the sampling schedules, see the Schedule of Assessments (Table 7).

Antibodies to MCPyV tumor antigens will be measured at baseline and end of treatment. Refer to the Laboratory Manual for instructions on sample procurement, processing, and shipping.

Formalin-fixed paraffinized archival tumor samples and optional fresh tumor biopsies will be assessed by immunohistochemistry for tumor cell SSTR2 expression and immune cell expression of proliferation, exhaustion, and other markers and for transcriptomics by Nanostring.

13.4. Biobanking Samples

Additional exploratory genetic, cellular, and/or serum markers of potential future interest may be explored if evidence of therapeutic activity is seen with XmAb18087. For biobanking, blood obtained for flow cytometry will be sent to Navigate BioPharma, where serum, PBMCs, and extracted nucleic acid will be aliquoted and stored at -70 °C. Biobanking is voluntary and requires specific subject consent.

14. STATISTICAL EVALUATION

14.1. Sample Size and Power

This study is being performed in 3 parts: MCC monotherapy (Part A), MCC combination therapy (Part B), and SCLC monotherapy (Part C). No formal power analyses were performed for efficacy endpoints for the initial dose escalation cohorts. After identification of each RD, Part A, Part B, and Part C will enroll expansion cohorts using a 2-stage design (Schultz, 1973).

In Part A, up to 9 subjects will be enrolled at the RD. If at least 1 subject shows a response by RECIST 1.1 criteria, then enrollment will continue up to a total of 22 subjects. A true response rate of 40% has statistical power of 84% to rule out a lower inactivity rate of 16% with a one-sided Type I error rate of 5%.

In Part B, up to 12 subjects will be enrolled at the RD. If at least 4 subjects show a response by RECIST 1.1 criteria, enrollment will continue up to a total of 30 subjects. A true response rate of 67% has statistical power of 84% to rule out a lower inactivity rate of 43% with a one-sided Type I error rate of 5%.

In Part C, up to 9 subjects will be enrolled at the RD. If at least 1 subject shows a response by RECIST 1.1 criteria, then enrollment will continue up to a total of 30 subjects.

Subjects who are not evaluable may be replaced. Up to 142 subjects will be enrolled. The total number of subjects enrolled will depend upon the number of safety run-in cohorts required to identify the RD for each Part. A true response rate of 30% has statistical power of 82% to rule out a lower inactivity rate of 11% with a one-sided Type I error rate of 5%.

14.2. Statistical Methods

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated clinical study report.

Unless otherwise specified, continuous variables will be summarized with N (ie, sample size), mean, median, standard deviation, minimum and maximum, and discrete variables will be summarized with frequencies and percentages. Safety and efficacy summaries will be performed for Parts A, B, and C separately and, for safety, also for the combined arms. For each Part, summary tables will be provided for each dose cohort and for the dose cohorts combined.

14.3. Study Endpoints

14.3.1. Primary Endpoints

The primary endpoints are as follows:

- Safety of (1) XmAb18087 monotherapy in MCC and SCLC, and (2) XmAb18087 and pembrolizumab combination therapy in MCC, as assessed by the following:
  - Incidence of treatment-emergent AEs (TEAEs)
  - Incidence of clinically significant changes in safety laboratory tests, PE findings, vital signs, and ECGs

  - Incidence and severity of CRS
- Efficacy of (1) XmAb18087 monotherapy in MCC and SCLC, and (2) XmAb18087 and pembrolizumab combination therapy in MCC using RECIST 1.1 assessment of CT/MRI imaging, as well as aggregate data, for the following:
  - ORR
  - CR rate
  - PR rate

14.3.2. Secondary Endpoints

The secondary endpoints are as follows:

- Efficacy of (1) XmAb18087 monotherapy in MCC and SCLC, and (2) XmAb18087 and pembrolizumab combination therapy in MCC using RECIST 1.1 assessment of CT/MRI imaging, as well as aggregate data, for the following:
  - Duration of response
  - PFS
  - OS
- PK characterization of XmAb18087, when administered as monotherapy and in combination with pembrolizumab, based on the parameters of C_{max}, time to reach maximum concentration (t_{max}), half-life ($t_{1/2}$), area under the serum concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), clearance (CL), volume of distribution (Vd), and volume of distribution at steady state (Vd_{ss}). Further details will be defined in a PK analysis plan.
- Assessment of immunogenicity by incidence of anti-XmAb18087 antibodies and qualitative assessment of safety outcomes
- PK characterization of pembrolizumab, when administered in combination with XmAb18087, based on parameters similar to those for XmAb18087, with further details to be provided in a PK analysis plan.

14.3.3. Exploratory Endpoints

The exploratory endpoints are as follows:

- Assessment of peripheral blood for cell surface markers by flow cytometry and similar bioanalytical methods that evaluate the response of selected immune system cells following administration of XmAb18087 as a monotherapy and in combination with pembrolizumab, including changes in lymphocyte subsets and in T-cell activation and exhaustion markers
- PD characterized by NETSPOT (gallium 68 dotatate) PET/CT results and by tumor-cell expression of SSTR2 and PDL1 and tumor-infiltrating immune-cell expression of PD1/PDL1 and other markers by immunohistochemistry, in response to administration of XmAb18087 monotherapy and in combination with pembrolizumab

- PD: IHC SSTR2 panel
- PD: MCC and SCLC IHC panels
- Correlation of clinical/radiographic response with MCPyV serology (MCC subjects only)
- Additional exploratory genetic, cellular, and/or serum markers of potential future interest. If evidence of therapeutic activity is seen with XmAb18087, biobanked samples may be assessed for genetic and immunologic factors that might predict response or nonresponse (optional part of study and may be reported separately from the clinical study report). Samples will not be retained for more than 15 years.

14.4. Analysis Populations

The populations defined below will be used for analysis:

- **Safety population**: All subjects who are enrolled and receive at least 1 infusion of XmAb18087.
- **Evaluable population**: All subjects who are enrolled, receive at least 1 cycle (Parts A and C: 6 doses XmAb18087, Part B: 5 doses XmAb18087 and 1 dose pembrolizumab) of XmAb18087 and have at least 1 postbaseline RECIST 1.1 assessment of tumor imaging available.
- **PD population**: All subjects who are enrolled, receive at least 1 dose of XmAb18087 (and 1 infusion of pembrolizumab, when relevant for a particular PD assessment), and have at least 1 preinfusion and 1 postinfusion set of biomarker data available for analysis.
- **PK populations**: All subjects who are enrolled and receive at least 1 dose of XmAb18087 (ie, the XmAb18087 PK population) or 1 infusion of pembrolizumab (ie, the pembrolizumab PK population), and have at least 1 set of postinfusion PK data available for analysis.

Continuous data will be presented using descriptive statistics: number of subjects (N), mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage, where the percentage is presented in brackets to 1 decimal place. Safety and efficacy summaries will be provided for the monotherapy and combination therapy arms separately, as well as for the combined arms.

14.5. Subject Characteristics and Disposition

The SAP will define analysis parameters for the study and takes precedence over this protocol section.

Demographic (age, gender, ethnic origin, race) and baseline characteristics (eg, height, weight, body mass index, ECOG performance status, etc.) will be summarized, as will disease-related characteristics (including any available genetic data), prior anticancer therapy, and relevant supportive care therapies.

A summary of subject disposition will include the following:

- Number of subjects enrolled
- Number of subjects who received treatment
- Number of subjects who complete the study treatment (1 cycle)
- Number of subjects who terminated treatment and reason for discontinuation of treatment
- Number of subjects who complete 6-month and 12-month follow-up period
- Number of subjects who terminated study and reasons for study terminations

14.6. Safety Assessment

Safety variables will include AEs, PE findings, vital signs, ECGs, and laboratory values.

The extent of exposure to XmAb18087 monotherapy, as well as exposure in combination with pembrolizumab, will be summarized by dose cohort based on the number of infusions administered and the number of treatment cycles completed, as well as the total dose received. Additional summaries of drug exposure will be provided based on the PK parameters described in Section 13. Reasons for missed infusions or early permanent discontinuation of XmAb18087 will be reported.

Summary tables and listings will be provided for all reported AESC.

Adverse events will be coded using the latest version of MedDRA. The verbatim term recorded by the Investigator will be mapped to System Organ Class (SOC) and Preferred Term using MedDRA.

Treatment-emergent AEs are defined as events with onset dates on or after the start of study treatment or events that are present before the first infusion of XmAb18087 and subsequently worsen in severity.

Adverse-event-related endpoints include the following:

- TEAEs
- Treatment-emergent SAEs (TESAEs)
- Treatment-related TEAEs (for XmAb18087 or for pembrolizumab, if they can be distinguished)
- Treatment-related TESAEs (for XmAb18087 or for pembrolizumab, if they can be distinguished)
- TEAEs by severity that are defined by NCI-CTCAE, Version 5.0
- TEAEs resulting in the permanent discontinuation of XmAb18087 and/or pembrolizumab.

All AE-related endpoints will be summarized by MedDRA SOC and preferred term. At each level of summation, subject will be counted once under the greatest severity and strongest study drug relationship. All AEs will be included in the listings.

The hematology, chemistry, and other laboratory values and change from baseline values will be summarized descriptively for each scheduled assessment time point and grouped by dosing cohort. The baseline value for each laboratory value is defined as the last assessment performed on or prior

to the date of first dose of study treatment. The toxicity grades for laboratory tests will be based on NCI-CTCAE Version 5.0 criteria. The use of blood transfusions (platelets, RBCs) and/or growth factor support will be reported. Similar analyses will be done for chemistry tests (including liver and renal function tests). Subject listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in the subject listings and will include flags for high and low values.

Vital sign results (blood pressure, pulse, respirations, temperature, and blood oxygen saturation by pulse oximetry) and change from baseline values will be summarized descriptively for each scheduled time point. The baseline value for each vital sign measurement is defined as the last assessment performed on or prior to the date of first dose of study treatment. Additionally, the vital signs measured immediately (within 60 minutes) before each infusion of XmAb18087; at 15, 30, and 60 minutes from the start of the infusion (± 5 minutes for each time point); immediately (within 5 minutes) before EOI; at 15, 30, and 60 minutes after the EOI (± 5 minutes for each time point); and then hourly (± 5 minutes) for 3 hours postinfusion will be summarized. The change of vital signs values from preinfusion will be summarized for each postinfusion point. Preinfusion assessments are defined as last vital assessment prior to the same infusion. Subject listings of all vital data collected during the study will be presented.

Electrocardiogram values and change from baseline values will be summarized descriptively for each scheduled time point. Subject listings of all ECG data collected during the study will be presented.

14.7. Efficacy Assessment

The objective of these analyses is to explore the effects of XmAb18087 when administered repeatedly as a single agent across a range of dose levels, in combination with pembrolizumab, and at RD for each Part of the study.

The assessment of antitumor effects of XmAb18087 will be based on response criteria defined in RECIST 1.1 (Appendix A).

The number and percentage of subjects achieving a best overall response of complete response (CR; confirmed and unconfirmed), partial response (PR; confirmed and unconfirmed), stable disease, progressive disease, and not evaluable will be presented.

Overall response rate is defined as subject's best response of PR or better. The number and percent of subjects who achieved ORR will be summarized. Two-sided exact 95% confidence intervals for the ORR will be determined using the binomial distribution. The duration of objective response will be calculated from the time of initial response (PR or better) to the first documentation of relapse (recurrence after CR) or progression (after PR).

The evaluable population defined in Section 14.4 will be used for summary of ORRs and duration of response.

Depending on the completeness of the available follow-up data, an analysis of PFS, measured relative to Day 1, will be performed based on the Kaplan-Meier method. Median time and its 95% confidence interval, as well as the 25^{th} and 75^{th} quartiles with their 95% confidence intervals, will be summarized. Progression will be determined using the criteria described in RECIST 1.1 (Appendix A). The date of progression is defined as the date of progression or death.

The date of censoring for subjects who end the study without documented progression will correspond to the date the last tumor assessment was performed. Subjects who terminated from study without postbaseline tumor assessment will be censored at Day 1.

Progression-free survival will be presented based on the safety population for the overall study.

The potential antitumor effects of XmAb18087 may also be evaluated in other subgroups of subjects. The specifications for these and other similar analyses will be described in the SAP and supersedes any protocol specifications.

14.8. Pharmacokinetic Analysis

Pharmacokinetic parameters including C_{max}, t_{max}, $t_{1/2}$, $AUC_{0-\infty}$, CL, Vd, and Vd_{ss} will be estimated using either noncompartmental or compartmental methods, whichever best describes the observed data. Pharmacokinetic parameters for XmAb18087 will be compared with and without pembrolizumab administration.

Pharmacokinetic parameters at presumed steady-state will include area under the serum concentration-time curve during a dosing interval (t; AUC_t; where t is 1 week), steady-state concentration (C_{ss}), minimum steady-state concentration ($C_{min,ss}$), steady-state fluctuation in concentrations (%Fluct), time of minimum concentration (t_{min}) and predicted accumulation (accumulation index, AI). The observed accumulation will be computed as the ratio of C_{max} and AUC_t at presumed steady state versus C_{max} and AUC_t after the first dose. Trough concentrations (C_{trough}) at predose will be used to evaluate the approach to steady state.

All PK parameters will be computed using actual elapsed time to PK sampling event and to dose event start and stop, calculated relative to the first dose start of infusion and the dose start for each infusion. Dose used to compute PK parameters will be the actual dose delivered during the infusion duration.

Dose proportionality across dose levels will be characterized by plotting C_{max} and $AUC_{0-\infty}$ and AUC_t versus dose. Similarly, the kinetic parameters $t_{1/2}$, t_{max}, CL, Vd, and Vd_{ss} across dose levels will be characterized by plots of these parameters versus dose.

Exploratory analyses may be performed to evaluate the relationship between 1 or more of the estimated PK parameters and selected safety, efficacy, and other serum protein assessment parameters described previously. The serum profile of XmAb18087 versus time will be evaluated with respect to any antibodies to XmAb18087 that may accelerate clearance.

A similar analysis of Pembrolizumab PK will be performed and details of both analyses will be described in a PK Analysis Plan.

14.9. Immunogenicity Assays

The incidence and titer of anti-XmAb18087 ADA will be reported by dose cohort and sample collection time point.

15. DIRECT ACCESS TO SOURCE DATA/NOTES

The Investigator or institution shall provide direct access to source data and documents for study-related monitoring, audits, IRB/Independent Ethics Committee (IEC) review, and regulatory inspection.

The Sponsor or its designee will monitor the study according to GCP guidelines. The PI and study center will permit the Sponsor, its representatives, FDA, and other regulatory agencies direct access to all original source data and documents for study monitoring audits and inspections. All requested information must be entered into the eCRF in the EDC database. The completed eCRF must be promptly reviewed and electronically signed and dated by the PI.

The PI may be subjected to a field audit by the Sponsor, ICON, and/or FDA inspectors in order to validate the participation of subjects in the study and to verify the data reported in the clinical database. The Sponsor should be notified immediately of any audits scheduled by any regulatory authorities. Copies of audit reports from regulatory authorities should be promptly forwarded to the Sponsor.

The Sponsor and PI uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data collected and analyzed by the Sponsor will be identified only by an identification number.

ICON will provide the study sites access to the EDC database that will be used to collect the required subject eCRF data for this trial. The eCRF must be supported by the corresponding information in the source document.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Conduct of the Study

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its representatives may conduct a quality assurance audit.

The study shall be performed in a manner that will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP, and applicable regulatory requirements.

The study will be conducted in compliance with the following:

- The protocol
- Ethical principles of the Declaration of Helsinki (Version 2013) and its amendments
- The principles of the GCP provided in the ICH Harmonized Tripartite Guidelines for GCP 1996
- FDA regulations (Code of Federal Regulations [CFR], Sections 312.50 and 312.56)
- All applicable national laws and regulations including but not limited to country-specific GCP

Any significant protocol deviations must be documented on the eCRF.

16.2. Study Monitoring

The Sponsor or its designee will monitor the study according to GCP guidelines. The PI and study center will permit the Sponsor, its representatives, FDA, and other regulatory agencies direct access to all original source data and documents for study monitoring audits and inspections. All requested information must be entered into the eCRF in the EDC database. The completed eCRF must be promptly reviewed and electronically signed and dated by the PI.

During the study, a Xencor monitor or representative will have regular contacts with the investigational site for the following:

- Provide information and support to the investigators.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to ICON or Xencor.

- Confirm AEs and SAEs have been properly documented on CRFs, that any SAEs have been forwarded to ICON, and that those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The Monitor will be available between visits if the Investigator(s) or other staff need information or advice.

The PI may be subjected to a field audit by the Sponsor, ICON, and/or FDA inspectors in order to validate the participation of subjects in the study and to verify the data reported in the clinical database. The Sponsor should be notified immediately of any audits scheduled by any regulatory authorities. Copies of audit reports from regulatory authorities should be promptly forwarded to the Sponsor.

The Sponsor and PI uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data collected and analyzed by the Sponsor will be identified only by an identification number.

ICON will provide the study sites access to the EDC database that will be used to collect the required subject eCRF data for this trial. The eCRF must be supported by the corresponding information in the source document.

17. ETHICS

17.1. Institutional Review Board/Independent Ethics Committee

The PI will submit the protocol, protocol amendments, ICF, Investigator's Brochure, and any subject recruitment materials to the IRB/IEC for approval, as required by 21 CFR, Part 56.

It is required that a valid IRB/IEC approve, in writing, the conduct of this clinical study, together with the Investigator's ICF, prior to study initiation. Until written approval by the IRB/IEC has been received by the Sponsor, no subject may undergo any procedures solely for the purpose of determining eligibility for this study.

The PI must provide study progress reports to the IRB/IEC at least annually for all IND studies or more frequently if required by applicable guidelines, regulations, or institutional procedures.

The PI must promptly notify the IRB/IEC of any SAEs occurring at the site, as well as any IND safety reports reported to the FDA, regardless of the reporting site location.

The Sponsor reserves the right to amend the protocol during the course of the study. It is the PI's responsibility to obtain IRB/IEC approval of any protocol amendments and to implement them in a timely manner. Protocol amendments in the form of an administrative letter signed by the PI should be submitted to the IRB/IEC for review. All protocol amendments must have IRB/IEC review and approval prior to implementation.

If a protocol amendment substantially alters the study design or increases the potential risk to subjects, the ICF must be revised and submitted to the IRB/IEC for review and approval. The revised ICF must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment and for all subsequent subjects prior to enrollment.

Documentation of IRB/IEC approval of the protocol, ICF, and other applicable study documents must be provided to the Sponsor or its agent, ICON, before commencement of this study. Copies of all study-related correspondence between the PI and IRB/IEC must be maintained in the site regulatory binder.

17.2. Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP as outlined in CPMP/ICH/135/95 and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR Parts 50, 56, and 312]).

The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present at the study site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

17.3. Written Informed Consent

The PI(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also

be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The PI is responsible for ensuring that subjects sign an appropriately approved ICF prior to enrolling the subject in the study. Any required signatures must be obtained before conducting any study procedures.

Each subject must sign a statement that he/she has given consent for the subject's participation in the study that complies with the requirements of 21 CFR Part 50. A copy of the signed ICF must be provided to the subject, another copy kept with the study records, and the original kept with the subject's medical records. In addition, the medical records will include documentation of the informed consent process.

A sample of any ICF to be used in this study that has been approved by the IRB/IEC must be forwarded to the Sponsor or its agent, ICON.

17.4. Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. Any deviations should be agreed on by both the Sponsor and the Investigator, with the appropriate written and approved protocol amendments made to reflect the changes agreed upon. Protocol amendments must be released by the responsible staff and receive IRB/IEC approval prior to implementation (as appropriate). Where the deviation occurs for the well-being of the subject, the Sponsor must be informed of the action agreed upon.

Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated clinical study report. All amendments will be distributed to all study protocol recipients with appropriate instructions.

17.5. Subject Confidentiality

Adequate records have to be maintained for the study, including but not limited to subject medical records, eCRFs, laboratory reports, worksheets, nursing notes, signed ICFs, product forms, SAE forms, and information regarding subject discontinuation and reasons for discontinuation. The confidentiality of each record with subject identification is to be guaranteed by the clinical Investigator.

18. DATA HANDLING AND RECORD KEEPING

18.1. Case Report Forms/Source Data Handling

The Investigator shall be provided with standardized case report forms (CRFs) and shall ensure that all data from subject visits are promptly entered into the CRFs in accordance with the specific instructions given. The Investigator must sign each CRF to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory.

The Investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and PE reports.

Data to be recorded directly on the CRFs (ie, no prior written or electronic record of data) and considered to be source data must be identified in the protocol.

18.2. Retention of Essential Documents

The Investigator or institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

18.3. Principal Investigator's Record Requirements

The PI shall retain study drug disposition records, copies of CRFs (or electronic files), and all source documentation (such as original ECG tracings, laboratory reports, and inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted or for the period specified by the Sponsor, whichever is longer. The PI must contact the Sponsor prior to destroying any records associated with the study. If the PI withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another PI or the IRB/IEC. Notice of such transfer will be provided in writing to the Sponsor.

19. PUBLICATION POLICY

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without receiving approval from the Sponsor in advance. Authorship criteria for all publications of Xencor-sponsored clinical trials are based on the International Committee of Medical Journal Editors guidelines, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, 2010). Authorship credit can be granted only to those who make substantial contributions to the publication.

At a minimum, study results will be published on www.clinicaltrials.gov on all primary and secondary outcomes, no later than 1 year after completion of the study (including completion of the study if it has been terminated early).

This protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The PI agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from the Sponsor. Results obtained from this study are the property of the Sponsor.

20. LIST OF REFERENCES

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APPENDIX A. RECIST GUIDELINES

RECIST GUIDELINES

Selected Definitions and Tables from Revised RECIST Guidelines (Version 1.1)

1. **Measurability of tumor at baseline**

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

1.1 Measurable tumor lesions

Lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest X-ray

2. **Measurability of lymph nodes at baseline**

- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

3. **Nonmeasurable lesions**

Nonmeasurable lesions are all other lesions, including the following:

- Small lesions (longest diameter < 10 mm or pathological lymph nodes with P10 to < 15 mm short axis) as well as truly nonmeasurable lesions
- Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

4. **Response criteria**

4.1 Target lesions

- A maximum of 5 target lesions may be identified and assessed for response.
- The following definitions are used to determine objective tumor response for target lesions.

1. Complete Response (CR): Disappearance of all target lesions
   - Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
2. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters

3. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
4. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

4.2 Nontarget lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol. The following tumor response definitions apply to the group of nontarget lesions:

- Complete Response (CR): Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limit
- Progressive Disease (PD): Unequivocal progression of existing nontarget lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)

4.3 New lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI of the brain which reveals metastases. The subject’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

5. Evaluation of overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. On occasion a response

may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response.

The subject's overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions.

This is captured in Table 13 (below).

Table 13: Assessment of Overall Response in Subjects with Target (± Nontarget Disease)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Sources:

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APPENDIX B. ECOG PERFORMANCE SCALE

Table 14: ECOG Performance Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

ECOG=Eastern Cooperative Oncology Group.

APPENDIX C. PROPHYLAXIS AND MANAGEMENT OF NAUSEA AND VOMITING AND HYPERSENSITIVITY REACTIONS, CYTOKINE RELEASE SYNDROME, AND NEUROLOGICAL TOXICITY

Prophylaxis and Management of Nausea and Vomiting

The Xencor Medical Monitor ([redacted]) should be contacted immediately by email or phone if questions arise concerning the grade of an infusion reaction. [redacted] email is [redacted], and his telephone number is [redacted].

Because administration of XmAb18087 has been associated with nausea and vomiting and with mild symptoms of infusion reaction/CRS in some subjects, the following prophylactic medications are to be administered for all subjects before at least the first [redacted]:

[redacted]

If a subject experiences nausea and/or vomiting despite prophylaxis, [redacted] are recommended for treatment of the symptoms.

Sites may also choose to use other/additional antinausea/vomiting medications for prophylaxis or treatment of symptoms, according to their practice and assessment of the subject's responses.

Guidelines for Prophylaxis and Management of Hypersensitivity Reactions, Cytokine Release Syndrome, and Neurological Toxicity Attributed to XmAb18087

Because administration of XmAb18087 has been associated with symptoms of infusion reaction/CRS in some subjects, it is required that all subjects receive the following medications before at least the first 4 doses of XmAb18087:

c. Acetaminophen (Tylenol®): 650 mg PO once before dosing with XmAb18087
d. Diphenhydramine (Benadryl®): 50 mg PO once before dosing with XmAb18087
e. 10 to 20 mg IV dexamethasone (Decadron®) before dosing with XmAb18087

If a subject receives 4 consecutive doses of XmAb18087 without ≥ Grade 1 infusion reaction/CRS, the prophylaxis described above may be modified, prophylactic medications are to be administered to all subjects before at least the first 4 doses of the study drug.

Introduction and Grading

Grading of toxicity, including allergic/hypersensitivity reactions, is by CTCAE version 5.0, except for CRS, which is using the ASTCT CRS Consensus Grading (Lee, 2019). See Table 15 for these definitions.

All sites should review and implement the general guidelines for the use of tocilizumab and IV fluids discussed below. Otherwise, management of CRS and other infusion-related reactions

should be per standard investigational site procedures. Or, if there are no local standards or if they are incomplete, the approaches discussed here may be used.

Table 15. American Society for Transplantation and Cellular Therapy Cytokine Release Syndrome Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[b]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.
Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading.
[a] Fever is defined as temperature ≥ 38 °C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5 °C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

Cytokine Release Syndrome Versus Allergic or Hypersensitivity Reactions

Cytokine release syndrome is mechanistically different from allergic/hypersensitive reactions (Lee, 2014), although some of the manifestations are common to both AEs and both have been reported to occur with therapeutic antibodies. An acute infusion reaction is often caused by a type 1 hypersensitivity mechanism due to IgE-mediated release of histamines and prostaglandins, although a direct interaction with mast cells and basophils can also occur. It is less clear how cytokine release is triggered, although it is likely to be associated with immune cell activation; in this case, there is evidence that immunologic cascade is initiated by triggering of CD3-expressing T lymphocytes, resulting in TNF-α mediated monocyte/macrophage activation and systemic toxic cytokine release (Li, 2019).

Signs and symptoms usually develop during or shortly after drug infusion in hypersensitivity reactions, are more likely to occur after several doses of the drug and are largely related to histamine release. Typical signs and symptoms of hypersensitivity reaction include rash/urticaria,

flushing, pruritus, fever, dyspnea, cough, and hypotension, although the following may also occur (Lenz, 2007):

- Arthralgia
- Bronchospasm
- Confusion, mental status changes, and/or delirium
- Dizziness
- Fatigue (asthenia, lethargy, malaise)
- Hallucinations
- Headache
- Hypertension
- Myalgia
- Nausea and/or vomiting
- Rigors/chills
- Diaphoresis
- Tachycardia

Cytokine release syndrome, on the other hand, is more likely to occur after the first dose or first escalated dose of drug than after subsequent doses. It may begin somewhat later and is more likely to be associated with hepatic and neurologic complications, including the following:

- Any of the hypersensitivity signs or symptoms listed above
- Aphasia or word-finding difficulty
- Elevated d-dimer and/or hypofibrinogenemia
- Fatigue (asthenia, lethargy, malaise)
- Gait disturbance/dysmetria
- Hallucinations
- Seizures
- Transaminitis and/or hyperbilirubinemia
- Tremor

The Xencor Medical Monitor should be contacted immediately if questions arise concerning the grade and/or treatment of the infusion reaction.

Treatment Guidelines for Cytokine Release Syndrome

Use of Tocilizumab for Cytokine Release Syndrome

Tocilizumab is a therapeutic antibody that interferes with binding of IL-6 to the IL-6 receptor. It has been used to decrease the severity and possibly mortality of severe CRS (Frey, 2017), and

early administration may be useful in improving outcomes. Below are suggested guidelines for its use:

- Sufficient tocilizumab (dose of 8 mg/kg) should be readily available to the area where subjects are receiving their infusions and being observed post infusion.
- Prompt tocilizumab therapy should be strongly considered if:
  - Oxygen saturation falls below 90% on room air, **OR**
  - Systolic blood pressure falls 20 mm Hg below predose measurements and below 100 mm Hg, **OR**
  - Temperature of > 38 °C (100.4 °F) in the presence of new or worsening dyspnea and/or tachypnea and/or rigors and/or tachycardia (HR > 110 bpm), **OR**
  - Early discovery of hepatic transaminase elevation. (Note that peak transaminase elevation appears to occur within 24 hours, so that it is unlikely that tocilizumab treatment on the day after study drug administration would affect the course or outcome in the absence of concurrent symptoms or signs of CRS).
- Repeat dosing of tocilizumab may be necessary if signs and symptoms persist or return after initial treatment.

Fluid Management

Cytokine release syndrome is sometimes associated with myocardial dysfunction, pulmonary edema, or capillary leak syndrome (Shimabukuro-Vornhagen, 2018). Although there are little or no data regarding use of anti-CD3 antibodies and the need for fluid management, it seems prudent to monitor subjects for weight gain and limit IV fluid administration in the acute setting.

- If a subject is noted to have had a ≥ 10% increase in body weight over the previous 2 weeks in association with new or significantly increased bilateral lower extremity edema, dosing should be delayed until this finding is evaluated and, if indicated, treated.
- For acute hypotension, an IV fluid bolus should be limited to 500 mL of normal saline or the equivalent.
- If there is not an adequate response to fluids, treatment with tocilizumab (and vasopressors, if necessary) should be considered rather than additional fluid boluses.

Cytokine Release Syndrome Treatment Guidelines by Grade

The following are treatment guidelines for XmAb18087 treatment-related infusion reactions (Lee, 2014); since it can be difficult to differentiate between different infusion reaction etiologies, both are included here.

Grade 1:

- Administer acetaminophen and/or diphenhydramine or dexamethasone to treat signs and symptoms if clinically indicated.
- Vital signs should be measured every 15 minutes or less as clinically indicated.

- Obtain a blood sample for cytokine analysis during the event and approximately 4 hours later, unless scheduled cytokine monitoring is already in progress.
- Monitor the subject for worsening of condition; if severity of event increases to a higher grade, stop the infusion, administer appropriate treatment, and refer to guidelines below for more severe infusion reactions.
- It may be useful to premedicate the subject with acetaminophen and antihistamines prior to the next infusion.

Grade 2:

- Hypotension responsive to fluids or a low dose of a single pressor, or mild respiratory symptoms treatable with low-flow oxygen are signs of Grade 2 toxicity. Older subjects or those with significant comorbidities may be at higher risk of decompensation in this situation.
- **Discontinue the infusion** and administer acetaminophen and/or diphenhydramine or dexamethasone to treat signs and symptoms if clinically indicated. Once symptoms have resolved, slow the infusion rate by 50% of the baseline rate. If after 1 hour, the subject's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes, as tolerated, to the baseline rate.
- Note that older subjects or those with significant comorbidities may be at higher risk of decompensation in this situation. When reactions occur in these vulnerable subjects, or in the case of rapidly escalating reactions, consider treatment with **tocilizumab** 4 to 8 mg/kg IV over 1 hour, with or without dexamethasone 10 to 20 mg IV (or equivalent).
- Vital signs should be measured every 15 minutes or less as clinically indicated. For subjects who are able to tolerate an increase in the infusion rate back to baseline and maintain normal blood pressure for 30 minutes after the rate increase then, at the discretion of the Investigator, the frequency of vital sign assessment may be reduced to every 30 minutes during the infusion.
- Obtain a blood sample for cytokine analysis during the event and approximately 4 hours later, in addition to scheduled cytokine monitoring if already in progress.
- Monitor the subject for worsening of condition; if severity of event increases to a higher grade, stop the infusion, administer appropriate treatment, and refer to guidelines below for Grades 3 and 4 infusion reactions.
- Subjects with maximum Grade 2 infusion reaction may continue on study and should receive prophylactic premedication with acetaminophen 650 mg PO and diphenhydramine hydrochloride 25 to 50 mg IV or PO prior to all subsequent XmAb18087 infusions.

Grade 3 and 4:

- **Stop the infusion** and disconnect the infusion tubing from the subject.

- Aggressive supportive care should be given immediately. Vasopressors, fluids, oxygen, epinephrine or bronchodilators, ventilatory support, antipyretics, and analgesics should be used as indicated.
- Treatment with tocilizumab 4 to 8 mg/kg IV over 1 hour with or without dexamethasone 10 mg IV (or equivalent) is strongly encouraged for CRS due to the high risk of progression and permanent organ dysfunction.
- Hospital admission for observations is almost always indicated, usually to an intensive care unit, since an initial appearance of improvement may quickly yield to rapid decompensation.
- Subjects with Grade 3 CRS or infusion reaction may be rechallenged once resolved. Subjects with recurrent Grade 3 or any Grade 4 infusion reaction should not receive further XmAb18087 treatment but will continue to be followed on the protocol (ie, for 4 weeks after last dose).
- Obtain a blood sample for cytokine analysis during the event and approximately 4 hours later, in addition to scheduled cytokine monitoring if already in progress.
- Obtain a sample for ADA testing as close to the onset of the event as possible, at the resolution of the event, and 28 days following the event.
- Notify the Xencor Safety Monitor or Xencor Medical Monitor, [redacted] (Telephone: [redacted]; Email: [redacted]), immediately.

Neurotoxicity

In addition to CRS, another toxicity observed after CAR-T cell therapy and CD3 bispecific antibodies is neurotoxicity. ICANS may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema (Lee, 2019). Neurotoxicity was previously considered in aggregate with CRS, but is now treated separately, due to its timing and response to treatment.

Neurologic symptoms may occur during or after CRS symptoms, but rarely precede CRS symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy. Headache is a nonspecific symptom, frequently occurring during fever or after chemotherapy in patients without other neurologic dysfunction. Thus, headache alone is not a useful marker of ICANS. Expressive aphasia, on the other hand, appears to be a very specific symptom of ICANS (Lee, 2019).

A consensus grading scheme, which is a slightly modified version of the CARTOX-10 screening tool, which incorporated key elements of the MMSE, the ICE score, will be used for the grading of ICANS (Table 9). It is important to note that the 10-point ICE screening tool is helpful for assessing patients for encephalopathy; however, the grading of ICANS requires assessment of the 10-point ICE score as well as evaluation of other neurologic domains, such as level of consciousness, motor symptoms, seizures, and signs of elevated ICP/cerebral edema, which may occur with or without encephalopathy. The ASTCT ICANS toxicity grading system is shown in Table 16. This grading scale will be used to assess neurotoxicity, rather than the CTCAE 5.0.

Table 16: Immune Effector Cell-associated Encephalopathy Scoring

ICE
Orientation: orientation to year, month, city, hospital: 4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
Attention: ability to count backwards from 100 by 10: 1 point

ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy (score).
Scoring: 10, no impairment;
7 - 9, Grade 1 ICANS;
3 - 6, Grade 2 ICANS;
0 - 2, Grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS (Lee, 2019).

Table 17: American Society for Transplantation and Cellular Therapy Immune Effector Cell-associated Neurotoxicity Syndrome Consensus Toxicity Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7 – 9	3 - 6	0 – 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy (score); ICP = intracranial pressure; N/A = not applicable; VI = sixth.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

[a] A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0 (Lee, 2019).

It has been speculated that high levels of IL-6 may directly mediate neurotoxicity in this situation (Lee, 2014).

Clinical management of neurotoxicity consists of the following:

- Monitor subjects closely for signs and symptoms of these events (including administration of mental status and neurologic examinations when these seem clinically warranted).
- If neurotoxicity becomes evident, a blood sample for cytokine analysis should be drawn at that time, and again 4 hours later, in addition to scheduled cytokine monitoring if already in progress.
- If neurologic toxicity is Grade 4, discontinue XmAb18087, if still infusing.
- For Grade 3 neurologic toxicity, withhold both drugs until the toxicity has recovered to ≤ Grade 1 (mild) and has remained at ≤ Grade 1 for at least 3 days before restarting therapy. Restart XmAb18087 at 75% of the previous dose. Restart pembrolizumab at the full dose. Escalate back to full dose at the time of the next dose if ≥ Grade 2 toxicity does not recur. If ≥ Grade 2 toxicity reoccurs at 75% dose, or if < Grade 2 toxicity takes more than 7 days to resolve, discontinue permanently.
- For severe neurologic symptoms, administer additional dexamethasone 10 mg intravenously and repeat every 12 hours if symptoms do not abate rapidly, or treat according to the clinical site's institutional protocol for such reactions.
- For recurrent seizures, anticonvulsant therapy may be necessary.

Appendix D. DOSE MODIFICATION AND TOXICITY MANAGEMENT FOR IMMUNE-RELATED ADVERSE EVENTS

IRAEs may occur shortly after the first dose of pembrolizumab or up to several months after the last dose. Based on existing clinical data for pembrolizumab and other checkpoint inhibitors, most IRAEs were reversible and could be managed with dose interruptions, administration of corticosteroids, and/or other supportive care. For suspected IRAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. IRAEs known to be associated with pembrolizumab, as well as guidelines for dose modification and management when they occur, are described in the Keytruda Prescribing Information (Keytruda® Package Insert, 2020); these guidelines are summarized in Table 18.

For additional information on diagnosis and management of IRAEs, see the NCCN Guidelines – Management of Immunotherapy-Related Toxicities (Appendix E).

Table 18: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events in Patients Receiving Pembrolizumab

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, it can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.
3. For severe and life-threatening IRAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if IRAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	IRAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
Immune-mediated hepatitis	AST or ALT greater than 3 but no more than 5 times the ULN or total bilirubin greater than 1.5 but no more than 3 times the ULN	Withhold	Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	IRAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
	In patients without liver metastases, AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN In patients with liver metastasis and Grade 2 AST or ALT at baseline, with an increase in AST or ALT of 50% or more relative to baseline that persists for at least 1 week	Permanently discontinue	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Immune-mediated endocrinopathies	Grades 3 or 4	Withhold until clinically stable	Administer corticosteroids and hormone replacement as clinically indicated	Monitor participants for signs and symptoms of endocrinopathies
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	Based on type and severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include, but are not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; IRAE = immune-related adverse event; IV = intravenous; ULN = upper limit of normal.

APPENDIX E. NATIONAL COMPREHENSIVE CANCER NETWORK AND AMERICAN SOCIETY OF CLINICAL ONCOLOGY: MANAGEMENT OF IMMUNOTHERAPY-RELATED TOXICITIES (IMMUNE CHECKPOINT INHIBITOR-RELATED TOXICITIES)

NCCN: Continuing Education

Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

Accreditation Statements

In support of improving patient care, National Comprehensive Cancer Network (NCCN) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: (1) review the educational content; (2) take the posttest with a 66% minimum passing score and complete the evaluation at **https://education.nccn.org/node/86963**; and (3) view/print certificate.

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Release date: March 10, 2020; Expiration date: March 10, 2021

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Management of Immunotherapy Related Toxicities
- Describe the rationale behind the decision making process for developing the NCCN Guidelines for Management of Immunotherapy Related Toxicities

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Management of Immunotherapy-Related Toxicities, Version 1.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Management of Immunotherapy Related Toxicities provide interdisciplinary guidance on the management of immune related adverse events (irAEs) resulting from cancer immu notherapy. These NCCN Guidelines Insights describe symptoms that may be caused by an irAE and should trigger further investigation, and summarize the NCCN Management of Immunotherapy Related Toxicities Panel discussions for the 2020 update to the guidelines regarding immune checkpoint inhibitor related diarrhea/colitis and cardiovascular irAEs.

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*Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower level evidence, there is uni form NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE-CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening as indicated	Clinical exam at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork • CBC with differential • Comprehensive metabolic panel	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required.	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis.
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)[c]	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 and free T4 if abnormal thyroid function suspected.
Adrenal/Pituitary (ICI_ENDO-4) • Adrenal: Serum cortisol (morning preferred)[c] • Pituitary: TSH, free thyroxine (T4)[c]	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (males), estradiol (females), adrenocorticotropic hormone (ACTH)
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Pulmonary function tests (PFTs) for high-risk patients	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy if needed to exclude other causes.
Cardiovascular (ICI_CARDIO-1) • Consider baseline EKG • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine phosphokinase (CPK)

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B).

[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

[c] After first four doses of immunotherapy, only as clinically indicated.

IMMUNO-1

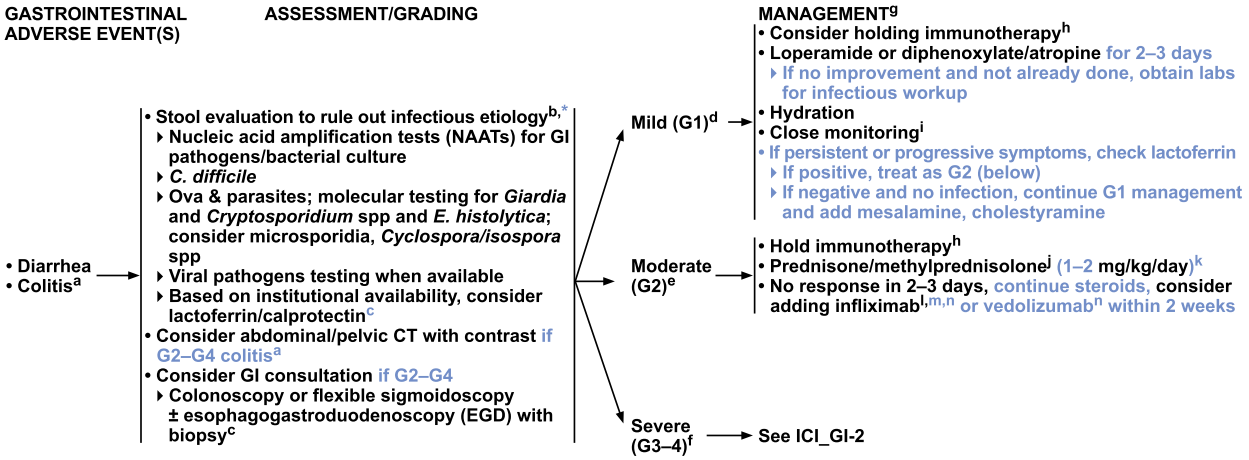
Overview

Immune checkpoints are part of the natural balance of the immune system to prevent autoimmunity and are exploited by cancer cells to suppress the immune response. Immune checkpoint inhibitors (ICIs) block proteins—namely PD-1, PD-L1, and CTLA-4—that allow tumor cells to evade detection and killing by T cells.[1–6] Since the FDA-approval of the CTLA-4 inhibitor ipilimumab in 2011, ICIs have become a treatment option for several advanced cancers. ICIs significantly improve overall survival and delay progression of tumors in patients with a variety of cancers.[7] Indications for ICIs have expanded dramatically and now include a wide array of cancer types.[1–8]

A major drawback of ICI therapy is the potential for immune-related adverse events (irAEs), which can affect any organ or tissue. The pharmacodynamics and pharmacokinetics of ICI immunotherapy differ greatly from those of cytotoxic chemotherapy or targeted anticancer therapy.[9] Traditional cytotoxic chemotherapy often results in acute-onset emetic and myelosuppressive effects, whereas irAEs tend to be relatively delayed in onset and inflammatory or autoimmune in nature.[10–13] Although the pathophysiology of ICI-related irAEs is not yet fully elucidated, knowledge regarding the role of immune checkpoint pathways in autoimmune disease provides some clues. Many autoimmune diseases are related to failure of T-cell tolerance and subsequent uncontrolled activation of immune effector cells. Early- and later-onset irAEs may result from distinct mechanisms that have yet to be elucidated. Typical earlier-onset, common irAEs appear to involve generalized epithelial inflammation and may be observed in the form of rash, colitis, and pneumonitis. Later-onset irAEs, which are typically less common, tend to be more-localized, organ-specific reactions. Research is ongoing into the specific mechanisms underlying irAEs associated with specific ICIs. The reported incidence of any-grade irAEs associated with single-agent ICI treatment ranges widely across agents and trials, from approximately 15% to 90%,[14,15] and patterns of toxicity may differ between specific ICI agents.[16] Severe irAEs leading to discontinuation of treatment have occurred in up to 13% of patients receiving anti–PD-1 monotherapy in clinical trials.[17–24] Although combination regimens offer the potential for enhanced efficacy, in general, observed toxicity with ICI-based combination regimens is greater than that for ICI monotherapy.

Recognizing Immune-Related Symptoms

Onset of irAEs can be immediate or delayed by as much as 2 years, and can affect any organ system.[25] Early

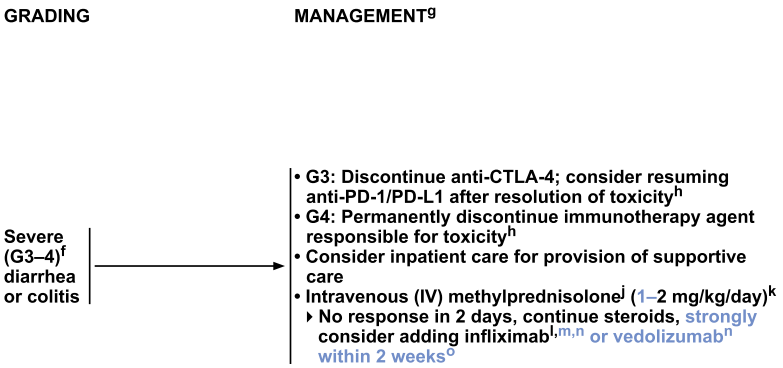


[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
[b] It is not necessary to wait for test results before providing therapy to manage immune-related adverse events (irAEs).
[c] If positive lactoferrin, strongly recommend early endoscopy or flexible sigmoidoscopy with biopsy within first 2 weeks of the onset of symptoms.
[d] Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[e] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[f] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).
[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] If progressive, consider stool evaluation to rule out infectious etiology.
[j] Convert to prednisone when appropriate.
[k] Treat until symptoms improve to Grade ≤1 then taper over <4–6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <4 weeks should be made to minimize the complication of infection.
[l] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A).
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Obtain TB test before receiving first dose of infliximab or vedolizumab.Treatment does not need to be held for results.
*Stool evaluation and all sub-bullets were added to the workup for G1.

ICI_GI-1

recognition of symptoms and prompt intervention are key goals for the successful management of immunotherapy-related toxicity. When encountering one or more of these symptoms, asking appropriate questions can help discern whether the patient is experiencing a symptom due to disease progression, an infection, some other condition, or an irAE. Symptoms that may cause clinical suspicion of an irAE include (main symptoms are bold and underlined; associated symptoms are underlined; possible irAE type/diagnoses are in italics):

- **Change in bowel pattern** compared with baseline, especially if it is watery diarrhea, stool contains blood or mucus, or cramping or severe abdominal pain develop, may indicate *colitis*. However, blood in the stools and/or fever may be because of other causes of gastrointestinal bleeding, such as *infection* or *peptic ulcer disease* or *bleeding due to tumor*.
- **Cough** may be due to an upper respiratory infection, but especially if the cough is dry or is coupled with shortness of breath, it could indicate *pneumonitis*.
- **Headaches** can be indicative of brain metastases, but when presenting with fatigue, visual symptoms, nausea, and other symptoms, may be indicative of *hypophysitis* (inflammation of the pituitary).[26,28] Headaches may also be indicative of *meningitis* when coupled with a stiff neck, photophobia, nausea, or fever. Headaches can also be indicative of *encephalitis* if coupled with fever, tiredness, confusion, mood change, memory problems, stiff neck, and other symptoms. Headaches, head pain, and scalp tenderness, may be indicative of *giant cell arteritis*.
- **Nausea** is a common symptom that can accompany certain cancer therapies. Nausea with abdominal pain/bloating could indicate *pancreatitis*. Nausea that occurs during infusion of an ICI, accompanied by fever/chills, hypertension, hypotension, sweating, myalgia, cough, or shortness of breath, may indicate an *infusion-related reaction*.
- **Rashes** are very common and may be accompanied by itching that can lead to scratching and severe *skin toxicities* causing edema, oozing, papulation, excoriations, lichenification, which may indicate *bullous dermatitis*, or separation of the dermis, a sign of *Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)*.
- **Fatigue** is a common symptom that alone or coupled with weight change, nausea, or other nonspecific symptoms may indicate a *thyroid disorder*,[26] *hypophysitis*, or,



[f] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).
[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k] Treat until symptoms improve to Grade ≤1 then taper over <4–6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <4 weeks should be made to minimize the complication of infection.
[l] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but optional. See Principles of Immunosuppression (IMMUNO-A).
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Obtain TB test before receiving first dose of infliximab or vedolizumab.Treatment does not need to be held for results.
[o] Fecal transplantation may be considered for immunosuppressant refractory colitis based on institutional availability and expertise.

ICI_GI-2

rarely, *adrenal insufficiency*.[28] Fatigue with tachycardia, palpitations, increased stool frequency, and other symptoms may be *thyrotoxicosis*.[27] Fatigue accompanied by nausea, chest pain, shortness of breath, arrhythmias, and other potentially nonspecific symptoms may be indicative of *myocarditis*. However, fatigue may also be attributed to depression, an infection, disease progression, a hematologic abnormality, or another condition.

- **Muscle** or **joint pain** may be indicative of *musculoskeletal toxicities*. Muscle pain alone or with fatigue, chest pain, and shortness of breath may be due to a *cardiac toxicity*, because myocarditis may occur concurrently with myositis.[29,32]
- **Muscle weakness** may be indicative of *neurologic toxicities*, such as *Guillain-Barré syndrome*, or, if coupled with vision changes, *myasthenia gravis*. Myasthenia gravis related to immunotherapy may be associated with myositis and myocarditis.[31,33,34]
- **Weight loss** and nausea may be due to disease progression, but may also indicate a *hepatic toxicity* or an *endocrine toxicity*.

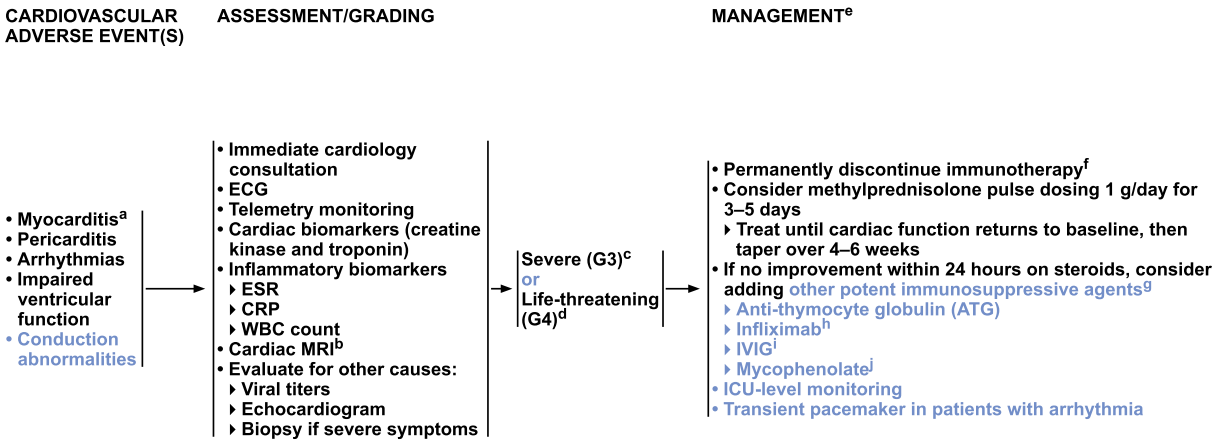
For many patients, routine laboratory monitoring, comparisons to baseline, and targeted questions by the treating healthcare providers will help identify some of the less common but serious irAEs. The primary facets of irAE management include early recognition and grading of toxicity, immunosuppression, and individualized modification to ICI administration. See the complete version of the NCCN Guidelines (available at NCCN.org) for management strategies for these and other ICI-related irAEs updated for 2020.

2020 Updates to the NCCN Guidelines

The NCCN Guidelines for Management of Immunotherapy-Related Toxicities provide guidance on the management of irAEs resulting from cancer immunotherapy, specifically ICI and CAR T-cell therapies. During the meeting to update the guidelines for 2020, the panel discussed updates to the management of many irAEs. These NCCN Guidelines Insights highlight recommendations for the assessment and treatment of ICI-related irAEs related to the gastrointestinal and cardiovascular systems.

Gastrointestinal Adverse Events: Diarrhea/Colitis

The most common gastrointestinal irAE presents as diarrhea and/or symptoms of colitis, which include watery



[a] Myocarditis symptoms are nonspecific. It is rare, but potentially severe, not viral in etiology, associated with myositis/myasthenia gravis, and is more common with combination therapy. In fatal cases, conduction abnormalities were mode of death and ejection fraction was preserved.
[b] No evidence specific to immunotherapy-related myocarditis; recommendations drawn from other causes of myocarditis.
[c] Arrhythmia, significant echo findings without hypotension, cardiac markers >ULN.
[d] Arrhythmia, hemodynamic instability (hypotension/cardiomyopathy), cardiac markers >3xULN.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Successful outcomes have been reported with other immunosuppressive agents, such as alemtuzumab or abatacept.
[h] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[i] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[j] Mycophenolate mofetil treatment (0.5–1 g every 12 hours).

ICI_CARDIO-1

diarrhea, cramping, urgency, abdominal pain, blood or mucus in the stool, fever, or nocturnal bowel movements. Diarrhea and/or colitis are the second most commonly reported AEs with ICIs, and symptoms typically develop within 6 to 8 weeks of starting treatment.[35,36] These gastrointestinal irAEs have been reported more frequently with anti–CTLA-4 monotherapy than with PD-1/PD-L1 inhibitors. In studies of CTLA-4 blockade, diarrhea has been reported in up to half of patients, with incidence typically reported between 30% and 40%.[14,37] The highest rates of ICI-mediated diarrhea/colitis have been observed with the addition of a PD-1/PD-L1 inhibitor to CTLA-4 blockade.[38–40]

Detection, Initial Assessment, and Grading of Diarrhea/Colitis

To facilitate early detection of diarrhea/colitis, patient education is key. It is important to determine the patient's baseline bowel habits prior to initiation of immunotherapy. Patients are encouraged to report changes in their bowel habits to the treatment team in order to facilitate early detection of colitis that may occur before the next scheduled clinic visit (see IMMUNO-1, page 232). Most cases present as diarrhea (increased frequency of bowel movements), but as described earlier, a variety of other colitis symptoms often occur. Severity of the diarrhea (ie, increase in number bowel movements per day compared with baseline) and the presence and severity of other colitis symptoms determine the grade of the gastrointestinal irAE (Table 1). Hemodynamic instability and life-threatening complications (eg, ischemic bowel, perforation, toxic mega-colon) may be associated with high-grade gastrointestinal irAEs. Table 1 shows grading for these adverse events, based on elements from CTCAE version 5.0 (colitis, enterocolitis, diarrhea),[41] Brahmer et al,[42] and additions from the NCCN Panel (see ICI GI-1 footnotes, page 233).

Stool evaluation to rule out infectious etiology, specifically *Clostridium difficile,* ova, parasites, and viral pathogens, is an important element of workup for patients with suspected immunotherapy-related diarrhea and/or colitis. For patients presenting with grade 1 diarrhea (increase of <4 bowel movements per day above baseline) and no symptoms of colitis, some panel members defer stool testing until diarrhea has persisted and not improved with conservative treatment (loperamide or diphenoxylate for 2–3 days), or symptoms

Table 1. Grading[a] for Colitis/Diarrhea[b]

	Terms **Diarrhea:** increase in frequency and/or loose or watery bowel movements **Colitis:** inflammation of the colon **Enterocolitis:** inflammation of the small and large intestines
Grade 1	• Increase of <4 bowel movements per day above baseline • Mild increase in ostomy output compared with baseline • No symptoms of colitis (watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements)
Grade 2	• Increase of 4–6 bowel movements per day above baseline • Moderate increase in ostomy output compared with baseline • Mild/moderate colitis symptoms: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements • Limiting instrumental ADLs[d]
Grade 3	• Increase of >6 bowel movements per day above baseline • Severe increase in ostomy output compared with baseline • Severe colitis symptoms: watery diarrhea, incontinence, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, ileus, nocturnal bowel movements, peritoneal signs • Limiting self-care ADLs[e] • Hemodynamic instability • Hospitalization indicated

Grade 4	• Same as grade 3, but with:
	  • Other serious/life-threatening complications (eg, ischemic bowel, perforation, toxic mega-colon)
	  • Urgent intervention indicated

Abbreviation: ADLs, activities of daily living.
[a]For all adverse events, grade 5 is defined as death.
[b]Definitions incorporate elements from CTCAE version 5.0 (colitis, enterocolitis, diarrhea),[41] Brahmer et al, 2018,[42] plus additions from the NCCN Panel (ICI GI-1 footnotes, page 233).
[d]Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, managing money, etc.
[e]Self-care ADLs include bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

have progressed (frequency of bowel movements increased and/or colitis symptoms developed). Blood or mucus in the stools, fever, and/or other symptoms of colitis (watery diarrhea, cramping, urgency, abdominal pain, nocturnal bowel movements) should prompt a thorough workup for infection, including stool evaluation. Patients presenting with blood in the stool should also be evaluated for other causes of gastrointestinal bleeding, including peptic ulcer disease and malignant bleeding, among others (eg, diverticulosis, angiodysplasia, hemorrhoids, ischemia). Diarrhea/colitis associated with immunotherapy can rapidly increase in severity, and therefore therapy to manage these gastrointestinal irAEs can be initiated while awaiting test results.

Measurement of fecal lactoferrin and calprotectin, 2 markers of inflammation, should also be considered as part of initial workup, depending on institutional availability. Calprotectin provides a quantitative measure of inflammation; low levels indicate mild inflammation or normal endoscopy and high levels correlate with ulceration.[43] Fecal lactoferrin is a noninvasive, qualitative biomarker that can predict colitis risk.[44,45]

For patients who present with diarrhea/colitis grade 2 or higher (as defined in Table 1), abdominal/pelvic CT with contrast and gastrointestinal consultation for further evaluation (ie, colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy [EGD] with biopsy) should be considered. Symptom-based grading (listed in Table 1) may guide prompt initiation of therapy (eg, steroids); however, imaging and biopsy results can help establish the etiology of the problem and assess the likelihood that more aggressive management approaches will be needed. Although retrospective case reviews suggest that symptom grade may not correlate with colitis severity as observed by endoscopy and histology,[46,47] results from a recent retrospective study suggest that lactoferrin results may be used to inform prioritization of endoscopy.[43] This study found that among patients with immune-mediated diarrhea/colitis, lactoferrin levels were strongly correlated with inflammation observed by endoscopy (70% sensitivity), and even more strongly correlated with inflammation detected by histologic evaluation of endoscopy biopsy specimens (90% sensitivity).[43] Histologic findings were correlated with the need for intravenous steroids and/or infliximab/vedolizumab for irAE management.[43] Early endoscopy, defined as ≤7 days after onset of immune-mediated diarrhea/colitis compared with >7 days, was associated with significantly shorter duration of symptoms (47 vs 19 days; P .026) and shorter steroid treatment duration (49 vs 74 days; P .053),[43] presumably because earlier endoscopy triggered earlier initiation of management. Performing endoscopy ≤30 days from onset of diarrhea/colitis (vs >30 days) was associated with significantly shorter duration of steroid treatment, a trend toward shorter duration of symptoms, and a significant reduction in recurrence of symptoms (50% vs 21.8% of patients; P .001). Better outcomes for patients who undergo endoscopy within 30 days of onset may be due to the earlier initiation of infliximab/vedolizumab (15 vs 31 days from onset; P .030). Given the results of this recent study,[43] early endoscopy with biopsy within the first 2 weeks of the onset of symptoms is strongly recommended for all patients with positive lactoferrin results, even those who have only grade 1 symptoms (per Table 1). Fever and tenderness upon abdominal examination may be an indication of bowel perforation warranting immediate imaging and treatment.

Management of Mild (Grade 1) Events

For patients presenting with mild diarrhea (grade 1, defined as an increase of <4 bowel movements per day) with no other symptoms of colitis (Table 1), the NCCN Guidelines recommend hydration, considering holding immunotherapy, and monitoring the patient closely to determine whether diarrhea is worsening or other

symptoms of colitis develop (see ICI GI-1, page 233). Loperamide or diphenoxylate/atropine may be used, although some panel members prefer to wait before starting, out of concern about obscuring signs of worsening diarrhea, which may delay initiation of treatment (eg, steroids) that actually reverses underlying immunotherapy-related inflammation, if present. If diarrhea persists or progresses, or no improvement is seen after 2 to 3 days of loperamide or diphenoxylate/atropine, tests for infections workup should be obtained and levels of fecal lactoferrin should be checked if not already done. Cases of grade 1 diarrhea (increase of <4 bowel movements per day) with no other symptoms of colitis, documented absence of infection, and a negative lactoferrin result, may be managed conservatively (hydration and loperamide or diphenoxylate/atropine), with the addition of mesalamine or cholestyramine, if necessary. If lactoferrin results are positive, however, endoscopy should be strongly considered, if not already performed, even if the only symptom is grade 1 diarrhea. Patients with a positive lactoferrin result and persistent/progressive diarrhea should be treated as those with moderate (grade 2) diarrhea/colitis (see next section), because these cases are likely to require more aggressive management, even if the diarrhea has not yet reached the grade 2 threshold (increase of ≥4 bowel movements per day above baseline) and no other colitis symptoms have yet developed.

Tools for Management of Grade 2 or Higher Events

Corticosteroids are typically the first line of treatment of diarrhea/colitis of grade 2 or higher. In retrospective reviews of patients with ICI-related diarrhea/colitis, symptoms resolved with corticosteroid treatment in approximately half of individuals.[36,46,48] However, for some cases, corticosteroids fail to control symptoms and the diarrhea/colitis may persist or worsen and become life-threatening in the absence of more aggressive management.

Infliximab is a monoclonal anti–tumor necrosis factor alpha (TNF-α) antibody used for treating various autoimmune diseases, including Crohn's disease, ulcerative colitis, rheumatoid and psoriatic arthritis, and psoriasis.[49–51] Infliximab has become a commonly used agent for treating steroid-refractory irAEs that develop during ICI therapy.[25,52] Case studies report on the successful use of infliximab for treating severe, steroid-refractory colitis associated with ipilimumab.[48,53,54] An FDA-approved biosimilar is an appropriate substitute for infliximab.

Vedolizumab is an integrin antagonist that binds to α4β7 integrin, blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), inhibiting the migration of T cells across the endothelium into inflamed gastrointestinal tissues. Vedolizumab is currently indicated for treating gastrointestinal inflammation due to ulcerative colitis and Crohn's disease.[55,56] Case reports have described the use of vedolizumab for the treatment of ICI-induced diarrhea/colitis.[56–58] Vedolizumab binds to gut homing lymphocytes and may provide more specific immune suppression for the inflamed gastrointestinal mucosa, thereby theoretically avoiding suppression of antitumor immune responses.

Introduction of either infliximab or vedolizumab within 10 days of onset of colitis can reduce the duration of symptoms and improve steroid taper success.[59] Treatment with ≥3 doses of infliximab or vedolizumab, and achieving endoscopic or histologic remission are associated with lower risk of colitis relapse. This is important because endoscopic remission is often a better predictor of a cure than clinical remission, in which cases repeat endoscopy may be helpful.

Case studies suggest that transplantation of fecal microbiota from healthy donors may resolve cases of diarrhea/colitis that are resistant to corticosteroids, infliximab, and vedolizumab.[60]

Management of Moderate (Grade 2) Diarrhea/Colitis

For moderate diarrhea/colitis (grade 2), defined as an increase of 4 to 6 bowel movements per day above baseline and/or mild to moderate symptoms of colitis (as detailed in Table 1), the NCCN Guidelines recommend holding immunotherapy and administering prednisone/methylprednisolone (1–2 mg/kg/d) (see ICI GI-1, page 233). If no improvement is noted within 2 to 3 days of starting steroid treatment, the NCCN Guidelines recommend continuing steroids and considering adding infliximab (or FDA-approved biosimilar) or vedolizumab, preferably within 2 weeks from onset of diarrhea. A tuberculosis test (blood test preferred) should be obtained before administering the first dose of infliximab or vedolizumab, although treatment can be initiated before results are received.

Management of Severe (Grade 3–4) Events

For severe diarrhea/colitis (grade 3–4), defined as an increase of >6 bowel movements per day above baseline and/or severe symptoms of colitis (Table 1), inpatient care should be considered if needed to provide adequate supportive care (see ICI GI-2, page 234). Intravenous methylprednisolone, 1 to 2 mg/kg/d, should be administered. After improvement in diarrhea/colitis is noted, the steroid dose may be tapered, usually over 4 to 6 weeks (see later discussion). For diarrhea/colitis related to ipilimumab, the NCCN panel recommends permanent discontinuation if serious or life-threatening diarrhea/colitis occurs. For diarrhea/colitis associated with PD-1/PD-L1 inhibitors, therapy should be held for grade 3, with consideration of rechallenge upon resolution of symptoms

below grade 1. The immunotherapy agent(s) responsible for immune-related grade 4 diarrhea/colitis should be permanently discontinued.

If no improvement is noted within 2 to 3 days on intravenous methylprednisolone (1–2 mg/kg/d), the NCCN Guidelines recommend continuing steroids and strongly considering adding infliximab (or FDA-approved biosimilar) or vedolizumab, preferably within 2 weeks of onset, especially for patients with high-risk endoscopic features.[43] Fecal transplantation may be considered for colitis refractory to immunosuppressant therapy, based on institutional availability and expertise.[60]

Duration of Treatment of Immune-Related Diarrhea/Colitis

For disease monitoring after receiving colitis treatment, checking the levels of calprotectin provides a quantitative measure of inflammation; low levels indicate mild inflammation or normal endoscopy and high levels correlate with ulceration.[43] Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. Endoscopy has revealed colonic ulcerations more commonly in steroid-refractory cases.[36,46,48]

Retrospective analysis of patients with refractory diarrhea/colitis found higher infection rates among patients treated with long-duration steroids (>30 days). Long-duration corticosteroid without infliximab was associated with increased infection risk compared with short-duration steroid plus infliximab, suggesting that earlier nonsteroid immunosuppressive therapy may confer better outcomes.[47] If a systemic corticosteroid is given, treatment should be continued until symptoms improve to grade 1 or better, then dose tapered over 4 to 6 weeks. In cases in which infliximab or vedolizumab is used, a shorter taper may help minimize the complication of infection, provided that the diarrhea/colitis (or other concomitant irAEs) does not worsen during the taper. Intravenous methylprednisolone should be converted to oral prednisone when appropriate.

The duration of therapy with TNF-α blocker (infliximab) or integrin blocker (vedolizumab) is not clearly defined. Evidence supports the use of up to 3 doses (at weeks 0, 2, and 6) to reduce risk of recurrence and increase likelihood of endoscopic/histologic remission.[59]

Cardiovascular Adverse Events

Efforts to characterize cardiac irAEs associated with ICI therapy have begun to provide a better understanding of ICI-associated myocarditis. Case series reveal a variety of potential manifestations of cardiovascular irAEs, including myocarditis, pericarditis, arrhythmias, cardiomyopathy, cardiac fibrosis, heart failure, and cardiac arrest.[61–65] Data collected over 4 years from 8 sites revealed 35 cases of ICI-mediated myocarditis, which were compared with a sample of patients on ICI therapy without myocarditis.[62] Prevalence was 1.14% in this patient population, with a median onset of 34 days from initiation of treatment. However, recent evidence suggests that ICI-associated cardiovascular toxicity, myocarditis in particular, is more common than initially thought.[33,34,62,66]

Myocarditis symptoms are nonspecific, such as myalgia, shortness of breath, and chest pain, which could also be attributed to pneumonitis or other irAEs.[29] It is rare, but potentially severe, associated with myositis/myasthenia gravis, and is more common with anti–CTLA-4/anti–PD-(L)1 combination therapy. A recent report analyzed a total of 40 case reports describing cardiac irAEs and found that even with rapid assessment and initiation of immunosuppression, mortality was still high at 23%.[67] In fatal cases, conduction abnormalities were the mode of death and ejection fraction was preserved.

Cardiac irAEs have been associated with ipilimumab, pembrolizumab, and nivolumab. Based on multicenter registry data, myocarditis was observed more often in patients receiving combination ICI therapy and in those with diabetes.[62] Recent analysis of the WHO database revealed 101 individual case safety reports of severe myocarditis following initiation of ICI therapy.[34] Of these cases, 57% had received anti PD-1 monotherapy and 27% received combination PD-1/PD-L1 plus CTLA-4 inhibitor. For cases with available dosing information (n 59), 64% (n 38) had received only 1 or 2 ICI doses at the time of toxicity onset. Concurrent severe irAEs, most commonly myositis and myasthenia gravis, were reported for 42% of cases. Data on cardiovascular comorbidities were not available, but only 25% of patients with myocarditis were on medication to treat cardiovascular disease or diabetes.[34]

Preexisting cardiovascular pathology was identified in more than half of patients (5/8) in one case series.[61] Co-occurrence with noncardiac irAEs was also observed in >50% of patients. Corticosteroids and/or supportive care measures were helpful to improve symptoms in most cases, although permanent cardiotoxicity and fatalities also occurred despite intervention.[61] Myositis and myocarditis were observed to co-occur in a recent study of ICI-related fatalities. Notably, myasthenia gravis also co-occurred in 10% of fatal myocarditis cases.[33] Case reports of ICI-related myocarditis have reported irAE flare during steroid taper or ICI rechallenge.[68,69]

Management

Baseline EKG and individualized assessment in consultation with cardiology should be considered as indicated. Periodic testing should be considered for patients with abnormal baseline or symptoms (see IMMUNO-1, page 232).

Once a cardiac irAE is suspected, immediate cardiology consultation and intensive care unit–level monitoring is recommended (see ICI CARDIO-1, page 235). Assessment should include telemetry monitoring and electrocardiogram. Recommended laboratory testing includes cardiac biomarkers (creatine kinase and troponin levels) and inflammatory biomarkers (erythrocyte sedimentation rate, C-reactive protein level, and WBC count). To rule out other potential causes, evaluation may include viral titers, echocardiogram, or biopsy in the case of severe symptoms. When feasible, cardiac MRI may provide additional diagnostic information.[70]

Table 2 summarizes grading for cardiovascular adverse events that may be associated with ICI therapy, based on elements from CTCAE version 5.0 (myocarditis, pericarditis, ventricular arrhythmia),[41] Brahmer et al,[42] and additions from the NCCN Panel (see ICI CARDIO-1 footnotes, page 235). In the setting of severe (grade 3) cardiac irAE, arrhythmia may be accompanied by significant echocardiogram findings without hypotension, and cardiac biomarkers above the upper limit of normal (ULN). Life-threatening (grade 4) cardiac irAEs are denoted by arrhythmia, hemodynamic instability, and cardiac biomarkers >3 times the ULN. Transient pacemaker may be recommended in patients with arrhythmia.[67] Immunotherapy should be permanently discontinued for any grade 3 or 4 cardiovascular irAEs. The panel recommends methylprednisolone pulse dosing (1 g/d for 3–5 days). In a multicenter registry report, corticosteroids were administered in 89% of cases with myocarditis, with high-dose steroids resulting in better treatment response.[62] Elevated troponin and higher rates of major adverse cardiac events, which were defined as "the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block," were observed more commonly among patients who were treated with lower-dose corticosteroid.[62] The NCCN Panel recommends treating with steroids until cardiac function returns to baseline, then dose taper over 4 to 6 weeks.

Beyond treatment with high-dose steroids, there are few data to suggest the optimal subsequent therapy should steroids fail. Treatment options for both severe (grade 3) or life-threatening cases (grade 4) are the same given the rapid progression of cardiac irAE. If no improvement is noted within 24 hours, the addition of other potent immunosuppressive agents should be considered, such as antithymocyte globulin (ATG),[62,67,71–73] infliximab[61,67,71,74] or an FDA-approved biosimilar, intravenous immunoglobulin (IVIG),[67,73,75] or mycophenolate.[76]

ATG is a polyclonal antibody derived from lymphoid cell immunized horses or rabbits, which reverses immunotoxicity by inducing T-cell depletion. Data supporting use of ATG to treat myocarditis and arrhythmia are limited to a number of single case reports with favorable outcomes.[62,67,71] Infliximab has also been used in cases studies to treat cardiotoxicities,[61,67,71,74] but it is important to note that it is contraindicated for patients who have heart failure.[29,77] IVIG is used to reduce the levels of antibodies that may be causing damage. IVIG was successfully used in a case report of smoldering ICI-related myocarditis that initially responded to corticosteroids but flared upon taper,[68] and has been used for years in the setting of cardiac rejection.[73,75] Mycophenolate mofetil is an antiproliferative agent that is used for cardiac transplant patients.[76]

Two additional immunosuppressive agents may be used based on case studies. A case report of a patient on pembrolizumab with confirmed myositis–myasthenia gravis overlap syndrome with worsening cardiac arrhythmia after methylprednisolone, mycophenolate, plasmapheresis, and rituximab described a successful outcome after treatment with alemtuzumab,[65] a monoclonal antibody that binds to

Table 2. Grading[a] for Select Cardiovascular Events[b]

	Terms
	Myocarditis: inflammation of the muscle tissue of the heart **Pericarditis:** irritation to the layers of the pericardium (the protective sac around the heart) **Other cardiovascular irAEs:** arrhythmias, impaired ventricular function, conduction abnormalities
Grade 1	• Asymptomatic • Abnormal cardiac biomarkers (creatine kinase, troponin) • Abnormal ECG or physical findings (eg, rub) consistent with pericarditis
Grade 2	• Mild symptoms or symptoms with moderate activity or exertion: may include chest pain, myalgia, dyspnea, arrhythmia, palpitations, peripheral edema, pleural effusion, fatigue • Abnormal screening tests: cardiac biomarkers (creatine kinase, troponin), ECG • For arrhythmia: expedited cardiology evaluation indicated
Grade 3	• Symptoms at rest or with minimal activity or exertion, or new onset of symptoms: may include chest pain, myalgia, dyspnea, arrhythmia, palpitations, peripheral edema, pleural effusion, fatigue • Pericarditis with physiologic consequences (eg, pericardial constriction) • Cardiac biomarkers (creatine kinase and troponin) >ULN • Significant echocardiogram findings without hypotension
Grade 4	• Moderate to severe decompensation (worsening signs and symptoms): may include congestive heart failure, chest pain, myalgia, dyspnea on exertion, arrhythmia, palpitations, peripheral edema, pleural effusion, fatigue • Hemodynamic instability (hypotension/cardiomyopathy) • Cardiac biomarkers (creatine kinase and troponin) >3× ULN • Life-threatening • Urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support for myocarditis)

Abbreviations: ECG, electrocardiogram; irAEs, immune-related adverse events; ULN, upper limit of normal.
[a]For all adverse events, grade 5 is defined as death.
[b]Cardiovascular events that can be associated with cancer immunotherapy. Definitions incorporate elements from CTCAE version 5.0 (myocarditis, pericarditis, ventricular arrhythmia),[41] Brahmer et al,[42] and additions from the NCCN Panel (see ICI CARDIO-1 footnotes, page 235).

CD52 on some immune cells and leads to destruction of peripheral immune cells. Similarly, one case reported success using abatacept[78] (a CTLA-4 agonist that affects T cells and may lead to rapid inactivation of the normal immune response) in a patient receiving nivolumab who developed glucocorticoid-refractory myocarditis with concurrent myositis, who had also been treated with plasmapheresis.

Conclusions

Proper management of ICI-related toxicities requires early identification of potential irAEs in order to administer adequate treatment. Recent case studies and clinical experience have changed irAE management strategies, which have been incorporated in the 2020 update of NCCN Guidelines for Management of Immunotherapy-Related Toxicities. These NCCN Guidelines Insights provide context for topics that were discussed by the panel during the 2020 update meeting.

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