NCT #: NCT04590781

# STATISTICAL ANALYSIS PLAN

## DATE

29 AUGUST 2022

## VERSION

1.0

## 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)

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# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| BMI | body mass index |
| $C_{max}$ | maximum observed serum concentration |
| $C_{min[trough]}$ | trough concentration |
| CR | complete response |
| CRS | cytokine release syndrome |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| ICH | International Conference on Harmonisation |
| IV | intravenous |
| MCC | Merkel cell carcinoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | US National Cancer Institute |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PD1 | programmed cell death 1 |
| PDL1 | programmed cell death ligand 1 |
| PFS | progression-free survival |
| PK/PD | Pharmacokinetics/Pharmacodynamics |
| PR | partial response |
| RD | recommended dose |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| SAP | statistical analysis plan |
| SCLC | small cell lung cancer |
| SRC | Safety Review Committee |
| TEAE | treatment-emergent AE |

# 2. INTRODUCTION

This statistical analysis plan (SAP) describes the methods to be used for analysis and reporting of clinical data collected throughout the study. It is intended to supplement the study protocol (Version 1.0, 18 August 2020), which contains details regarding the design and conduct of the study. This plan should be read in conjunction with the study protocol and the electronic case report forms (eCRFs).

The study has been terminated early by the sponsor. Only 4 subjects have been enrolled in the study. No efficacy or pharmacokinetic-pharmacodynamic (PK-PD) analyses will be performed. Due to the small sample size, only demographics, baseline characteristics, safety, and efficacy listings will be generated.

# 3. STUDY OBJECTIVE(S) AND ENDPOINT(S)

## 3.1. Primary Objectives

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

## 3.2. Secondary Objectives

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 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 $C_{min[trough]}$) of pembrolizumab when co-administered with XmAb18087

## 3.3. Study Endpoints

Safety:

- Incidence of treatment-emergent adverse events (TEAEs)

- Incidence of clinically significant changes in safety laboratory tests, physical examination findings, vital signs, and electrocardiograms (ECGs)

- Incidence and severity of cytokine release syndrome (CRS)

Efficacy:

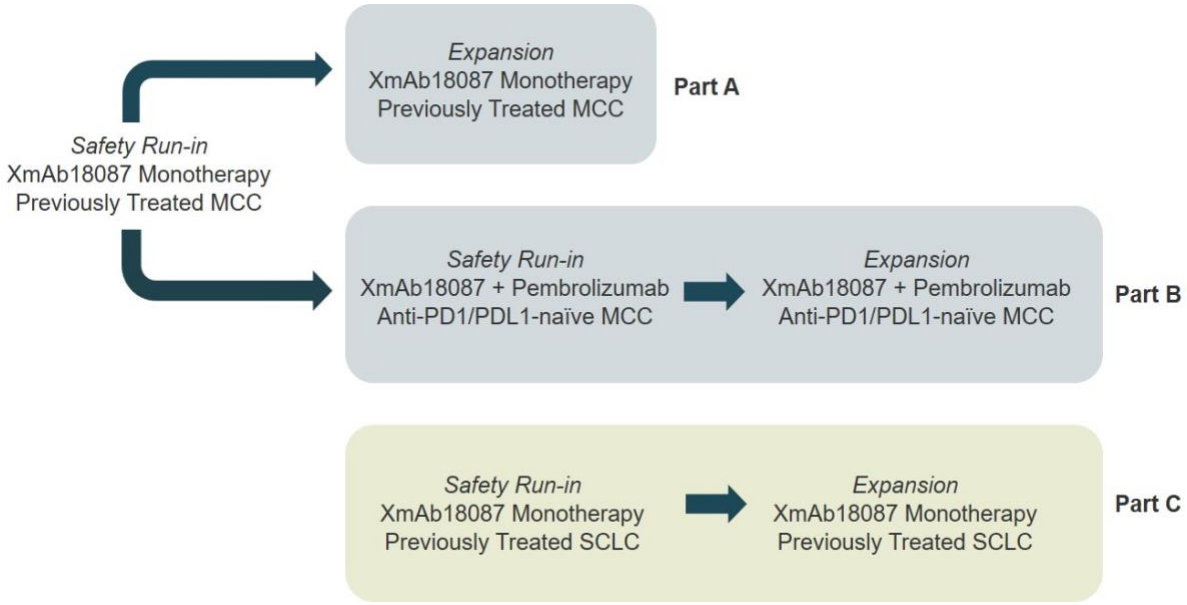
- ORR
- CR and PR rate
- Duration of response
- PFS
- OS

# 4. STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

## 4.1. Study Design

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 the figure below.

**Figure 1: 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 intravenously (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 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.

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 cytokine release syndrome (CRS) during inpatient admission will continue to be monitored as an inpatient for at least 24 hours after the symptoms have subsided.

## 4.2. Schedule of Assessments

See study protocol Section 7.9 Study Assessments.

# 5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

All data analysis output will be generated using SAS version 9.4 or later.

## 5.1. Changes in Planned Analyses from the Protocol

The study has been terminated early by the sponsor. Only 4 subjects (2 in Part A and 2 in Part C) have been enrolled in the study. No efficacy or PK-PD analyses will be performed. Due to the small sample size, only listings for demographics, baseline characteristics, safety, and efficacy assessments will be generated.

## 5.2. Derived and Transformed Data

### 5.2.1. Study Day

If the date of assessment occurs on or after the first dose date, then study day will be calculated as (date of assessment – date of first dose) + 1. If the date of assessment occurs prior to the first dose date, then study day will be calculated as (date of assessment – date of first dose). There is no study day 0.

### 5.2.2. Missing Data

Unless otherwise specified, missing data will be treated as missing, ie, no special handling/ missing data imputation will be performed.

#### 5.2.2.1. Partial/Missing Dates

For partial dates, the algorithms for imputation will vary depending upon the parameter; missing or incomplete medications start and stop dates will be imputed to determine whether the medications are taken concomitantly. Eg, missing adverse event (AE) start dates will be imputed to determine whether the adverse events are treatment emergent. In listings, all dates will be listed as recorded. The details of imputation rules can be found in Appendix 11.

# 6. STATISTICAL CONSIDERATIONS

## 6.1. Determination of Sample Size

This study was planned 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.

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%.

Due to the early termination of this study, only 4 subjects have been enrolled.

## 6.2. Interim Analyses

No formal interim analysis is planned.

## 6.3. Final Analyses

Final analysis will occur after all subjects have had their 28 days post-end of treatment visit.

# 7. 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.

# 8. DISPOSITION, DEMOGRAPHICS, BASELINE CHARACTERISTICS AND MEDICAL HISTORY

## 8.1. Disposition of Subjects

A listing will be provided including the analysis population, first and last dose date, and the dates of and the primary reasons for the end of study treatment and end of study.

## 8.2. Protocol Deviations

Protocol deviations will be documented by the clinical research associates and project manager on an ongoing basis throughout the study. Protocol deviations will be collected separately from (ie, external to) the eCRF database, and will be listed and discussed in the clinical study report.

## 8.3. Demographics and Baseline Characteristics

The baseline and demographic characteristics will be listed for each subject. It will include age, sex, race, ethnicity, reproductive history, height, weight, and BMI.

## 8.4. Medical History

General medical history will be listed including system organ class, preferred term, and start and end dates. Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher.

Initial diagnosis and prior disease-specific therapies will be listed separately.

# 9. TREATMENTS AND MEDICATIONS

## 9.1. Prior and Concomitant Medications

Prior medications are defined as medications that stopped before the date and time of the first dose; concomitant medications are defined as medications that are ongoing at the first dose or start after the first dose.

## 9.2. Extent of Exposure to Investigational Drug

Extent of exposure is defined as the total number of days a subject is exposed to investigational drug. Specifically, the duration will be calculated as (Date of Last Dose – Date of First Dose + 1).

## 9.3. Investigational Drug Compliance and Dose Intensity

Investigational drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of investigational drug as prescribed. The overall investigational drug compliance rate will be calculated as (the total number of doses administered / the total number of doses planned) ×100. The total number of doses planned is the total number of scheduled doses until the subject's last dose.

Relative dose intensity will be calculated as (the cumulative amount of study drug administered / the cumulative planned amount of study drug).

# 10. EFFICACY ANALYSES

Efficacy analyses will be based on the RECIST 1.1 tumor assessment. Due to the small sample size, only listings will be generated.

**Best Overall Response**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment.

**Duration of Response**

The duration of 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) or death. Patients who terminated the study without documented disease progression will be censored at the last radiological assessment date.

**Time to Initial Response**

Time to initial response is defined as time from first dose to initial response (PR or better).

**Time to Best Overall Response**

Time to best overall response is defined as time from first dose to best overall response. If there are multiple best overall responses, the earliest one will be taken.

**Progression-Free Survival (PFS)**

PFS is defined as the time from the date of first dose of study treatment until the date of progressive disease or death, whichever is earlier. Subjects who end the study without documented progression will be censored.

**Table 1: PFS Censoring Rules**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline tumor assessments | First Dosing visit (Cycle 1 Day 1) | Censored |
| Documented progression | Earliest of:<br>Date of radiological assessment showing new lesion(s) (if progression is based on new lesions);<br>or<br>Date of last radiological assessment of measured lesions (if progression is based on increase in sum of target lesions);<br>or<br>Date of last radiological assessment of nontarget lesions (if unequivocal progression occurs based on nontarget lesions) | Progressed |
| No progression | Date of last radiological assessment | Censored |
| Treatment discontinuation for undocumented progression | Date of last radiological assessment | Censored |
| Treatment discontinuation for toxicity or other reason | Date of last radiological assessment | Censored |
| New anticancer treatment started | Date of last radiological assessment | Censored |
| Death before first PD assessment | Date of death | Progressed |
| Death between adequate assessment visits | Date of death | Progressed |
| Death or progression after missing more than one tumor assessment visit | Date of death or progression | Progressed |

PD = progressive disease; PFS = progression-free survival.

**Overall Survival (OS)**

OS is defined as time from first dose till death from any reason. Subjects who terminate the study without documented death will be censored on the date of the last visit/contact.

# 11. SAFETY ANALYSES

## 11.1. Adverse Events

AEs and serious AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) (except CRS, which is graded using the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading) and be described using the MedDRA by system organ class, preferred term, severity, and relationship to XmAb18087.

Treatment-emergent AEs (TEAEs) will be marked. TEAEs 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.

## 11.2. Deaths

Listings will be provided to document all deaths on study, including those reported on End of Study and Long-Term Follow-Up/Survival Status eCRFs.

## 11.3. Clinical Laboratory Evaluations

Hematology, chemistry, coagulation, viral serology, and urinalysis laboratory values at each scheduled time point will be listed. Laboratory results outside predefined normal ranges and reported as clinically significant by investigators will be flagged in the data listings.

## 11.4. Physical Examination and Eastern Cooperative Oncology Group Performance Status

Physical examination results and Eastern Cooperative Oncology Group (ECOG) performance status results will be presented in separate data listings.

## 11.5. Vital Signs

Observed vital signs measurements at each scheduled time point will be listed for heart rate (beats/minute), respiratory rate (breaths/minute), systolic/diastolic blood pressure (mmHg), temperature (°C), and weight (kg).

## 11.6. Electrocardiograms

The ECG measurements at each study day will be listed for heart rate (bpm), PR interval (ms), QRS interval (ms), RR interval (ms), QT interval (ms), QTcF interval (ms), etc.

ECG interpretations will be reported as normal, abnormal not clinically significant, or abnormal clinically significant.

# 12. REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2):228-247.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials (E9); 1998 Feb 5.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline. Structure and content of clinical study reports (E3); 1995 Nov 30.

4. National Cancer Institute. Common terminology criteria for adverse events v5.0. NCI, NIH, DHHS; 2017 November 27.

5. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5(6):649-55.

# APPENDIX 1. IMPUTATION OF PARTIAL AND MISSING DATES

## Adverse Event

All AE start dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE start date is missing, but an AE end date is present and after the first dose date, then the AE start date will be imputed as follows for the purpose of determining treatment emergent flag only:

| Year of onset | Month of onset | Day of onset | Onset date to be imputed as |
|---|---|---|---|
| Missing | Missing | Missing | Set date to first dose date |
| year = year of first dose | Missing | Missing/Non-missing | Set month and day to those of first dose |
| year ≠ year of first dose | Missing | Missing/Non-missing | Set month and day to January 1 |
| year = year of first dose | Non-missing | Missing | Set day to the day of first dose |
| year ≠ year of first dose | Non-missing | Missing | Set day to first day of onset month |

If AE resolution date is present and prior to first dose date, then there is no need to impute incomplete AE start date, as the AE is not treatment emergent, and the event should be in the medical history.

## Concomitant Medications

- If year and month are present and day is missing, then set day to first day of the month for start date and set day to last day of the month for end date.
- If year and day are present and month is missing, then set month to January for start date and set month to December for end date.
- If year is present and month and day are missing, then set month and day to January 1st for start date and set month and day to December 31st for end date.
- Completely missing dates will not be imputed.

- If start date is completely missing and end date is on or after the first dose, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.

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| Envelope Summary Events | Status | Timestamps |
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| Certified Delivered | Security Checked | 8/29/2022 12:19:36 PM |
| Signing Complete | Security Checked | 8/29/2022 12:36:46 PM |
| Completed | Security Checked | 8/29/2022 6:44:23 PM |

| Payment Events | Status | Timestamps |
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