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Genmab

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Protocol No: GCT1044-01

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First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1044 in subjects with malignant solid tumors

Abbreviated Statistical Analysis Plan

Final Analysis of Escalation Parts

Version: v2.0

Date: 14DEC2021

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1 Introduction

1.1 Preface

The objective of this document is to detail the statistical methodology to be used for the planned analyses of the Escalation Part GCT1044-01, for the development of GEN1044 for the treatment of solid tumors (which induces T-cell mediated cytotoxicity of 5T4-expressing tumor cells by crosslinking CD3 on T cells with the tumor-associated antigen 5T4 on tumor cells).

This statistical analysis plan (SAP) is based on the following information and documents:

Trial Protocol	03 Apr 2020 – version 3.0 (Amendment 2)
Trial Protocol	30 Mar 2021; v4.0 (Amendment 3)
Unique Case Report Forms (CRFs)	07 Jul 2021 eCRF_Final_5.0

Layouts, programming notes and titles for the tables, listings and figures are further specified in the DPS.

1.2 Timing of statistical analyses

Upon review and evaluation of the overall safety profile and safety signals of GEN1044 on 29 September 2021, Genmab Safety Committee classified pneumonitis as an important identified risk for GEN1044. Given this, further enrollment was stopped into GCT1044-01.

GEN1044 was tested in with a prime dose, followed by up to one intermediate dose, and then full doses until treatment discontinuation. The data will be summarized by the cohorts presented in Table 1.

Table 1: Dose Escalation Cohorts

Cohort	Priming Dose (C1D1)	1st Intermediate Dose (C1D8)	2nd Intermediate Dose / Full Dose (C1D15)	Full dose (C2D1)
0.3/3/3 mg	0.3	3	3	3
1/5/5 mg	1	5	5	5
1/3/10 mg	1	3	10	10
1/3/30 mg	1	3	30	30
1/5/30 mg	1	5	30	30
1/10/30 mg	1	10	30	30
1/5/30/37.5 mg*	1	5	(30)	(37.5)
1/5/45 mg**	1	5	45	45
1/3/60 mg	1	3	60	60

[redacted]

2 Modification History

2.1 Changes to the trial protocol

Efficacy endpoints will only be listed by subject and timepoint, they will not be summarized in the CSR.

2.2 Changes to previous SAP versions

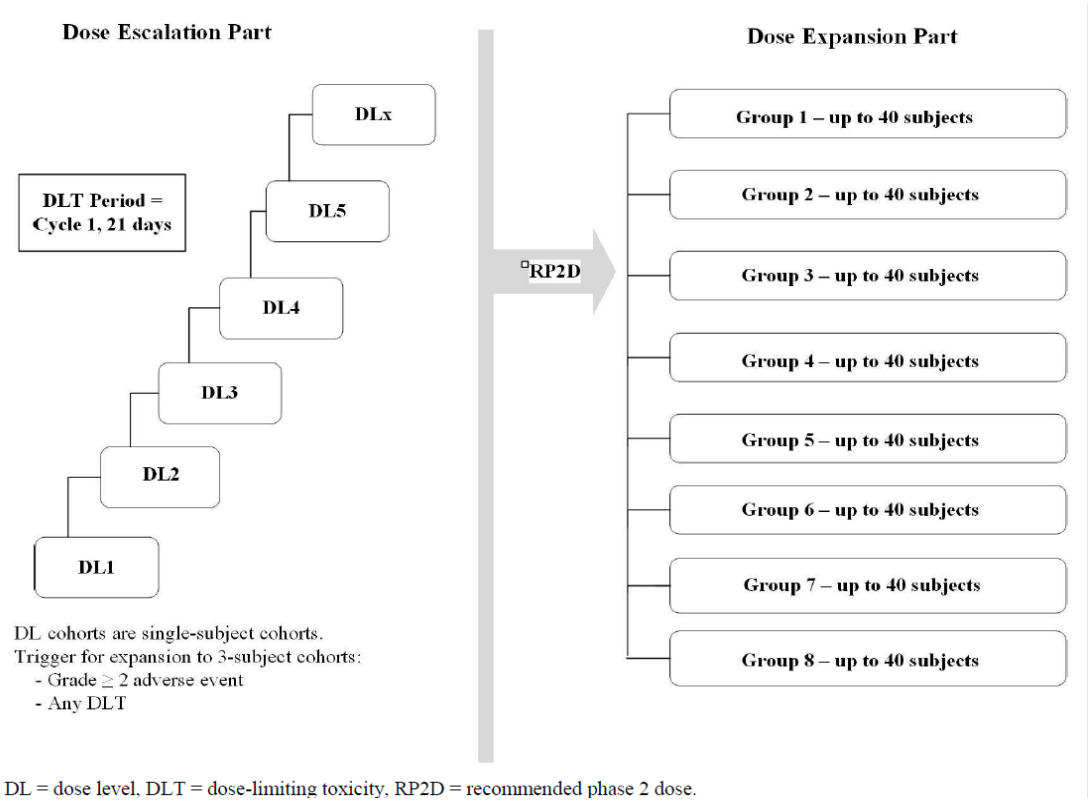
Due to the early termination of GCT1044-01 it was also decided to write an abbreviated CSR including key safety information (as would be included in a full CSR), whereas efficacy information and information in other sections should be concise and not as comprehensive as in a full CSR. Furthermore, all analyses for the expansion part were deleted as no expansion data was collected.

This SAP version describes the analysis required for the abbreviated CSR.

3 Trial Design

The conceptual trial design is visualized in Figure 1. The trial was planned as a two-part trial, with an escalation part followed by an expansion part. This analysis plan incorporates the planned analyses Escalation Part only, as required for the abbreviated CSR.

Figure 1 GCT1044-01 Trial Design



DL = dose level, DLT = dose-limiting toxicity, RP2D = recommended phase 2 dose.

In the Escalation Part, GEN1044 was administered by intravenous (IV) infusions at increasing dose levels, see Table 1.

3.1 Primary objectives and endpoints

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Determine recommended phase 2 dose (RP2D)	• Dose-limiting Toxicities (DLTs)
• Establish safety profile of GEN1044	• Adverse events (AEs) and safety laboratory parameters
Secondary	
• Establish PK profile	• PK parameters (clearance; volume of distribution; area under the concentration-time curve (AUC) from time zero to last quantifiable sample (AUC_{last}) and from time zero to infinity (AUC_{inf}); maximum (peak) observed serum drug concentration (C_{max}); time to reach maximum (peak) serum drug concentration (T_{max}); predose trough concentrations (C_{Trough}); and elimination half-life ($T_{1/2}$).
• Evaluate immunogenicity of GEN1044	• Anti-drug antibody (ADA) response
• Evaluate anti-tumor activity based on response assessment criteria (RECIST v1.1)	• Anti-tumor activity, ie, reduction in tumor size according to response assessment (RECIST v1.1): ○ Objective response rate (ORR) ○ Disease control rate (DCR) ○ Duration of response (DOR) ○ Time to response (TTR)
Exploratory	
• Assess pharmacodynamics and potential biomarkers of GEN1044	• Immune system activation (eg, T-cell activation, cytokine production, [redacted]), expression of tumor targets (eg, 5T4 [redacted] and potential biomarkers)
• Assess anti-tumor activity based on iRECIST	• Anti-tumor activity, ie, reduction in tumor size according to iRECIST ○ Immune ORR (iORR) ○ Immune DCR (iDCR) ○ Immune DOR (iDOR)
• For prostate cancer subjects only: Assess anti-tumor activity based on Prostate Cancer Working Group 3 (PCWG3)-Modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1	• Anti-tumor activity, ie, reduction in tumor size according to RECIST v1.1 modified by PCWG3 for bone lesions ○ Modified ORR (mORR) ○ Modified DCR (mDCR) ○ Modified DOR (mDOR) ○ Composite response rate (CRR)
• For prostate cancer subjects only: Assess changes in prostate-specific antigen (PSA) from baseline	• PSA response • PSA progression

3.2 Sample size

<u>Escalation Part</u>

The mBOIN design, as described in Section 4.2.1.1 of the protocol, will enrol up to 58 subjects. Enrolment may be halted based on the pre-specified stopping rules as described in Section 4.2.1 of the protocol.

The initial cohort size is single subject. The cohort size will be expanded to 3 subject cohorts if a DLT or Grade ≥2 AE within the first 21 days of Cycle 1 is observed in a single subject cohort. (After this, all subsequent cohorts are planned as 3 subject cohorts.) Further details are provided in Section 4.2 of the protocol.

3.3 Treatment administration schedule

GEN1044 will be infused intravenously in 21-day cycles, as per Section 4.1 of the protocol:

- Cycle 1-4: Day 1, 8, and 15
- Cycles 5 and later: Day 1 only

3.4 Treatment assignment

Subjects will be enrolled into pre-defined dose cohort during the Escalation Part.

4 Analysis Sets

Enrolled Subjects

Enrolled Subjects include all subjects whose treatment were assigned.

Full Analysis Set (FAS)

The full analysis set (FAS) and safety set are defined in the same way and will comprise all subjects who receive at least 1 dose of trial drug. All subjects will be classified according to the dose level and treatment schedule (if applicable) which they were assigned.

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Safety Set (SAF) / Treated Set

The Safety set is the same as the FAS.

Dose-Determining Analysis Set (DDS)

The Dose-Determining Set (DDS) includes all FAS subjects in the Escalation Part who meet the minimum exposure criterion and have sufficient safety evaluations or experience a DLT during the first 21 days of dosing (i.e., in Cycle 1).

A subject will meet the minimum exposure criterion if the subject takes at least 2 out of 3 pre-planned doses during the DLT period (such as 1 priming dose and 1 full dose).

A subject will have sufficient safety evaluations if the subject has been observed for ≥21 days following the first dose and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur.

Subjects will be analyzed according to the trial treatment received, as defined for the FAS.

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented by dose level cohort, for the different analysis sets as defined in Section 4.

In general, continuous variables will be summarised using descriptive statistics, i.e. displaying number of subjects in the respective analysis population, number of subjects with data, number of subjects with missing values, mean, standard deviation, minimum, median, and maximum.

Categorical variables will be summarised by using frequency counts and percentages. In addition, the number of subjects with missing values will be displayed where appropriate. When the number of subjects with non-missing values is displayed by visit (i.e., the number of subjects with a certain assessment completed at a given visit), that number will be used to calculate the percentages for that visit. Otherwise, the number in the column header (e.g., the number in that cohort, etc.) will be used as the denominator unless otherwise specified.

Means, medians, and standard deviations will be presented by 1 additional decimal place more than the standard presentation level of the respective subject data. Minimum and maximum values will be presented using the same number of decimal places as the subject data. Percentages will be presented to 1 decimal place if not otherwise stated.

If the number of subjects in a category is 0, then the percentage will not be displayed, and only a count of 0 will be shown.

Figures will be presented as necessary. Unless otherwise specified, by-visit figures will display information as presented in tables (e.g., based on analysis visit). Time-to-event figures, profile plots, and other figures not based on specific visits will include unscheduled visits.

Unless otherwise specified, all subject data collected as part of this trial (CRF data, laboratory results, etc.) will be presented in data listings. In general, data will be sorted by dose level cohort or tumor type cohort (as appropriate), site, and subject, and when appropriate by visit or other identifiers for sequence or type of observation.

5.2 Baseline values

The **baseline value** is defined to be the last non-missing value which was assessed before the first dose of investigational treatment.

5.3 Calculation of durations

Durations in months will be calculated as durations in days by dividing by 30.4375.

Time from initial diagnosis will be calculated in years, from the date of initial diagnosis to the date of the first dose date: (first dose date – date of initial diagnosis) /365

Total treatment duration will be calculated in days as:

- If last cycle is Cycle 1, 2, 3 or 4: last dose date – first dose date + 7
- If last cycle is Cycle 5 or later: last dose date – first dose date + 21

5.4 Missing data

Imputation of partial start date for Adverse Event and Medications

- if month and may are missing, and the year is same as the year of first dose, then assign the date of first dose as AE start date; else assign Jan 1st of the year.
- if only day is missing, and the month and year are same as the month and year of first dose, then assign the date of first dose as AE start date; else assign 1st day of the month.
- Compare the imputed date with the date of last known alive/contact; if the imputed date is bigger than the date of last known alive/contact, then assign the date of last known alive/contact as AE start date.

Imputation of partial end date for Adverse Event/Medications, and partial date of diagnosis:

- assign DEC 31st of the year if both Month and Day are missing.
- assign last day of the month if only Day is missing.
- Compare the imputed date with the date of last known alive/contact; if the imputed date is bigger than the date of last known alive/contact, then assign the date of last known alive/contact as AE end date.

5.5 Observation and analysis times

Subject information may be presented by cycle day or study day, as appropriate.

Study days

Study day is defined as the number of days between the first dose of trial medication and a particular date, and is calculated as:

- Study day = Assessment date – Date of first dose of trial medication, where assessment date is before the date of first dose
- Study day = Assessment date – Date of first dose of trial medication + 1, where assessment date is on or after the date of first dose

Therefore, the date of the first dose of trial medication will be Day 1, and the day immediately prior will be Day -1.

Trial periods

For the Escalation Part only, the DLT period is defined as the first 21 days of treatment, as per protocol 7.1. Therefore, this period will run from Cycle 1 Day 1 through Cycle 1 Day 21.

The trial participation period is divided into three mutually exclusive segments:

- The pre-treatment period includes information collected from the date of informed consent until the day prior to the first dose of trial medication. (Subjects not receiving trial medication will remain in the pre-treatment period for the duration of their participation.)
- The on-treatment period begins on the date of the first dose of trial medication and continues through the 30th day after the last dose of trial medication (i.e. if the last dose was on Day 1, the on-treatment period would continue through Day 30). The 30th day after last dosing is planned to coincide with the Safety Follow-up Visit.
- The post-treatment period begins at end of the on-treatment period + 1 day

If incomplete data makes it impossible to definitively assign an observation to one of these periods, the data will be conservatively assigned to the on-treatment period.

6 Subject Accounting and Disposition

6.1 Subject accounting

The number and percentages of subjects in each analysis set as defined in Section 4 will be presented by dose level cohort.

6.2 Disposition and withdrawals

The number and percentage of subjects will be summarized by dose level cohort including:

- Subject status: not yet begun treatment (for reporting subject status while trial is ongoing), on treatment, discontinued trial treatment, and withdrawn from trial
- Primary reasons for discontinuation from trial treatment, and discontinuation from trial
- Total number of days on trial

7 Demographics and Background Characteristics

Demographic and baseline characteristics, as specified below, will be presented descriptively. The DPS will present further details on what categories are included in below summaries.

7.1 Demographics and baseline characteristics

The following demographic characteristics will be presented:

- Sex
- Age (years), as entered on the CRF, continuously and categorized as <65 and >/= 65 years
- Race and ethnic origin, as entered on the CRF
- Ethnicity
- Weight (kg) at baseline

7.2 Disease characteristics

The following disease diagnosis will be presented:

- Primary diagnosis at Screening (uterine, prostate, etc.)
- Time from initial diagnosis to 1st dose (years)

7.3 Prior Anti-Cancer Therapy

- The following Prior Anti-cancer therapy will be summarized: the number of prior anti-cancer therapies (One prior line, Two prior lines, Three prior lines, ≥3 prior lines, and Missing)
- Type of prior therapies (Platinum-based therapy, Anti-EGFR therapy, Anti-PD-1/PDL1 therapy, Systemic therapy, Prior Radiotherapy, Prior surgery related to the disease)
- Best response to last prior cancer therapy (as collected in eCRF; CR, PR, SD, PD, NE)

8 Exposure and Compliance

8.1 Dose Level Cohorts

All subjects receiving investigational treatment during this open-label trial will receive GEN1044. Subjects in the Escalation Part will receive dose levels as assigned.

8.2 Dosage and Treatment Duration

Descriptive statistics for the number of cycles initiated, duration of treatment (days), number of dose administrated, cumulative dose administered (mg), Number of full dose, and Cumulative full dose (mg) will be presented overall and by dose level cohort.

Subjects with dose interruptions, dose reduced, and delay as well as reasons for these modification (adverse event, drug administration issues, or other), will be summarized by dose level cohort.

9 Safety

9.1 Primary safety analysis

Dose-Limiting Toxicities (DLTs)

The primary endpoint for the Escalation Part of this trial is the DLTs. Adverse events (AEs) that are assessed by the investigator to be at least possibly related to GEN1044, which occur during the DLT period of the Escalation Part. DLT will be summarized by PT in order of descending frequency using Dose-Determining Analysis Set.

The distribution of DLT occurring at the dose level will be plotted by subjects.

9.2 Adverse events (AEs)

AEs will be coded using MedDRA, and the National Cancer Institute Common Terminology Criteria for AEs (CTCAE criteria v5.0). Subjects will be included only once in incidence summary tables, presented by Preferred Term (PT) only.

- Adverse events collected during the pre-treatment period (see definition in Section 5.5) will be considered pre-treatment and included in listings (marked with a flag).
- Treatment-emergent adverse events (TEAEs) are defined as AEs which begin, or worsen, during the on-treatment period.
- Adverse events collected during post-treatment period may be tabulated separately from the TEAEs and provided in listings (marked with a flag).

The following summaries of TEAEs will be presented:

- TEAE overview
- TEAEs by PT, in order of descending frequency
- TEAE by SOC, PT and Worst Toxicity Grade, in order of descending frequency
- Related TEAEs, by PT, in order of descending frequency
- TEAE Leading to Withdrawal from Treatment by SOC, PT and Worst Toxicity Grade, in order of descending frequency
- Serious TEAEs, by PT, in order of descending frequency
- Fatal TEAEs (TEAEs resulting in death) by PT, in order of descending frequency

9.3 Adverse Events of Special Interest (AESI)

Cytokine Release Syndrome (CRS) events will be graded as per Lee et al 2019 and as described in Section 10.3.1 of the protocol. The summaries include:

- Subjects with at least one CRS Event (by maximum Grade)

- CRS signs and symptoms
- CRS Accompanied by tocilizumab use, leading to dose modification, leading to treatment discontinuation
- Time to first CRS Onset (days)
- Longest CRS Duration (days)

9.4 Death

The number and percentage of subjects died on study, death within 30 Days of last dose, death within 60 days of last dose, as well the number and percentage of subjects died due to each primary cause will be summarized.

9.5 Clinical laboratory results

Haematology and chemistry laboratory results will be graded programmatically using CTCAE 5.0.

The shift of CTCAE grade from baseline to the worst post-baseline grade will be summarized. If a test includes both Hyper- and Hypo- abnormal, then both CTCAE grades will be included in the summaries.

10 Cytokine and immunophenotyping measures

The absolute value of Cytokine, fold change from baseline of Immunophenotyping immune cell margination, and percentage change from baseline of Immunophenotyping T-cell activation will be summarized using descriptive statistics (mean, median, minimum, maximum, n, and standard deviation). Data will be summarized per planned time point during Cycle 1 only.

11 Treatment Response

The timepoint response is evaluated by investigator or qualified designee based on Imaging assessments using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The response data will be listed.

12 Software

The data will be analysed using SAS version 9.4 or higher.

13 Abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DDS	Dose-Determining Analysis Set
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DPS	Data Presentation Specification
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
IRR	Infusion-Related Reaction
mBOIN	Modified Bayesian Optimal Interval
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	Non-Small Cell Lung Cancer
NE	Not Estimable
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommend Phase 2 Dose
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TNBC	Triple-Negative Breast Cancer
TTNT	Time to Next Anti-Cancer Therapy
WHODRUG	World Health Organization Drug Dictionary

14 References

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