Signature Page for GCT1015-03_SAP
Study GCT1015-03 v2.0

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Study GCT1015-03 v2.0

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# Statistical Analysis Plan

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|---|---|
| Sponsor: | Genmab |
| Protocol Title: | A Multi-center, Open-Label Trial Investigating the Efficacy and Safety of Continued Treatment with Tisotumab Vedotin in Patients with Solid Tumors Known to Express Tissue Factor |
| Protocol Version: | Final version 5.0, dd. 24 September 2018 |
| Trial Code: | GCT1015-03 |

**For [redacted]:**

Author: [redacted], Senior Biostatistician

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**For Sponsor**:

Reviewers:

- [redacted], Biostatistician
- [redacted], Director, Clinical Research Scientist

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# Table of Contents



# 1. List of Abbreviations and Definition of Terms

| Abbreviation | Term |
|---|---|
| | |
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| BP | Blood Pressure |
| bpm | Beats per Minute |
| CA 125 | Cancer Antigen 125 |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IMP | Investigational Medicinal Product |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| WHO | World Health Organization |



## 2. Introduction

This Statistical Analysis Plan was written for the clinical trial GCT1015-03 conducted in Europe and the United States of America. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

## 3. Trial Design and Objectives

### 3.1 Trial Objectives

#### 3.1.1 Primary Objective

- To collect long-term safety data from patients with solid tumors who have been treated with tisotumab vedotin and completed any base trial (i.e., GEN701 or GEN702).

#### 3.1.2 Secondary Objective

- To further evaluate the anti-tumor activity of tisotumab vedotin.

### 3.2 Trial Design

The trial design is available in section 8.1 Overall Trial Design and Plan of the protocol final version 5.0 dd. 24 September 2018.

### 3.3 Sample Size Justification

Since the trial will include all patients willing to continue on treatment after completing other tisotumab vedotin trials (i.e., GEN701 and GEN702), no sample size determination can be made. It is expected that approximately 25 patients will enter the GCT1015-03 trial.

## 4. General Analysis Definitions

Data will be analyzed using SAS (Version 9.4 or higher).

Given the low expected number of patients and the heterogeneity between patients at entering this trial with regards to dosing regimen (as followed by the patient in the base trial), indication and response to treatment in the base trial, no formal statistical analyses are planned. Instead, all endpoints will only be listed. All enrolled patients will be included in the listings.

All data collected in this maintenance trial will be listed by base trial, dosing regimen (as followed by the patient in the base trial), indication, patient number and visit (if applicable). All listings will include the first IMP administration date in this trial and the last IMP administration date at the time of the database snapshot or database lock. Whenever applicable the reason for not done will be included in the listings.

When presenting coded data (e.g. medical history, concomitant medication, adverse events), the dictionary and the version used will be mentioned in the footnote. The current version of each dictionary will be used.

In case there will be a need for summary tables, these can be performed using descriptive statistics as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.



- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values.

The following data will be included from the base trials as specified in the respective sections below:

- Medical history data
- Local tumor assessments
- Exposure data

## 4.1 Trial Period and Visit Window Definitions

### 4.1.1 Trial Periods

Treatment period will be defined as the period between the date of first IMP administration in the base trial and the date of last IMP administration + 30 days or the date of the end of trial visit in this trial when available.

Trial periods will not be used in the analysis as the data is listed only.

### 4.1.2 Visit Windows

Visits will be reported as captured in the eCRF.

## 4.2 Planned Analyses

As this trial may be ongoing for a very long time, potentially several interim analyses may become relevant. Given that it is an open-label trial with no formal hypotheses, this will not require any formal methods such as control of the alpha level. It will simply consist of lists of what has been observed so far with tisotumab vedotin during the trial conduct.

## 4.3 Definition of Populations (Analysis Sets)

### 4.3.1 Enrolled Population

The Enrolled Population consists of all patients who sign the informed consent form (ICF).

## 4.4 Subgroup Definitions

Not defined at the time of final SAP given the objectives and the size of the trial.

## 4.5 Treatment Assignment and Treatment Arms

Tisotumab vedotin will be administered as an intravenous infusion on Day 1 of each 21-day cycle (once every three weeks [1Q3W]).

The dose will be 2.0 mg/kg or if dose reduced in the base trial continue the same dose. Dose reductions are allowed according to the protocol section 9.5.

## 4.6 Calculated Variables

Baseline is defined as the last assessment value before or on the date of the first IMP administration in this trial unless specified otherwise.



Date/time of first study treatment in the listings refers to first IMP administration in the base trial.

Study days for visit date, assessment date, date of progression and date of death are calculated versus the start of IMP administration in the base trial.

### 4.7 Partial/Missing Dates

Partial or missing dates will not be imputed as the data will only be listed. All information available will be presented.

### 4.8 Methods to Be Used For Handling Missing Data

All available data will be included in data listings and tabulations.

No imputation of missing data is planned.

### 4.9 Changes to Protocol

Summary tables might be created as needed.

## 5. Trial Patients

### 5.1 Disposition of Patients

Date of signing the ICF (including additional ICFs), version and date of ICF, base trial, last trial drug intake date in the base trial, screening failure and the reason, the primary reason for discontinuation of the trial including the reason for 'other' and the reason for withdrawal by patient, date of progression and date of death will be included.

A listing of all visits will be created including the reason for unscheduled visits and a flag if target/non-target assessment is done.

### 5.2 Protocol Deviations

The protocol deviations will be listed including a flag for major deviations.

Protocol violations will be defined in the protocol deviations plan.

### 5.3 Inclusion and Exclusion Criteria

Listing of all inclusion and exclusion criteria not met together with the protocol version will be provided.

## 6. Demographic and Baseline Disease Characteristics

In the listing of demographic characteristics, the variables to be listed are:

- Gender (Male/Female)
- Age (Years), date of birth
- Race (White, Black or African American, Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska native, Other + details)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- ECOG performance score (0-5). Note: at entry only patients with an ECOG performance score of 0 and 1 are allowed.



- Childbearing potential (Yes/No and reason)
- Cancer type (Ovary, Cervix, Endometrium, Bladder, Prostate, Head and neck, Esophagus, Lung)

## 7. Medical History

Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The medical conditions will be listed including term, system organ class and preferred term, start and end date, ongoing flag and started more than 1 year ago flag.

The medical history from the base trial will be reported.

## 8. Subsequent Cancer Therapies

All subsequent cancer therapies, except for surgeries, will be listed including the anatomical therapeutic chemical (ATC) code level 2 and active ingredient (WHO-DD dictionary). Surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented including system organ class and preferred term.

## 9. Prior and Concomitant Medications

Prior and Concomitant medications will be classified according to World Health Organization Drug Dictionary.

Medications will be flagged according to the following 3 distinct categories:

- Prior when they start and end before the first day of trial treatment.
- Prior and ongoing when they start before the first day of trial treatment and stop or continue after the first day of trial treatment.
- Medications will be reported as concomitant when they start on or after first day of trial treatment.

A listing of all medications recorded on the (prior and) concomitant medications CRF page will provide details including indication, dose, route, frequency, start and stop dates, prior/concomitant flag, active ingredient and ATC class.

## 10. Efficacy Evaluation

### 10.1 Anti-tumor Activity

Anti-tumor activity measured by tumor shrinkage (based on sum of the diameter(s) of all target lesions from the CT or MRI scan evaluations) will be listed. Details of target lesions (method, lesion location and specification, description, longest and shortest diameter), non-target lesions (method, lesion location and specification, description, lesion status and specification) and new lesions (method, lesion site and specification and description) will be included. Response assessments including the target lesion overall response, non-target lesion overall response, new lesion status, overall response and date of disease progression will be listed in a separate listing. Disease response or progression should be evaluated according to the current published RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 (Eisenhauer et al., 2009[1]). Baseline will be defined as the last assessment before the first IMP administration in the base trial.Local tumor assessment information available from the base trials will be included in these listings.



Results obtained from an independent, central imaging review will be included when available.

### 10.2 CA 125 (Ovarian cancer only)

CA 125 values over time including the change from baseline from the initial trial will be listed.

### 10.3 ECOG Performance Status

ECOG performance status results will be listed.

## 11. Safety Evaluation

### 11.1 Extent of Exposure

The listing of extent of exposure will include the treatment administration date and start and end times, the planned dose and planned total dose, dose adjusted (Yes/No) and reason (including AE and details for Other), actual dose administered, the actual volume infused, administration interrupted (Yes/No) including times and reason, planned dose administered (Yes/No) and reason if not and treatment label identifier. Number of infusions in this trial and in total since start in the base trial will be added as well as the cumulative dose since start of the treatment in the base trial.

Exposure information from the base trials will be included in the listing.

Ocular AE mitigation plan administrations in relation to infusions will be included in this listing.

### 11.2 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE criteria version 4.03, 2010).

Adverse events will be listed including the reported term (verbatim), system organ class and preferred term, start and end date/time, start and end day relative to the date of the start date of treatment in the base trial, outcome, toxicity grade, seriousness, relationship to the trial treatment and infusion, action taken and if supporting clinically significant laboratory results.

A flag will be added to mark if the AE occurs before the first IMP administration in this trial, or after the last IMP administration in this trial. In addition, flags will be added to mark ocular adverse events, overdose and medication errors and adverse events of special interest (Bleeding-related events, neuropathy and ocular events).

### 11.3 Deaths and Serious Adverse Events

The same listing as above will be repeated for:

- Serious AEs
- Fatal AEs
- NCI CTCAE Grade 3/4 AEs
- AEs leading to discontinuation of the IMP
- Non-serious grade 2 or higher ocular events.



All deaths will be listed separately including the source CRF page (fatal AEs, reason for withdrawal on End of trial form) and the death date.

### 11.4 Neuropathy and Skin Assessment

Neuropathy and skin assessment data will be listed.

### 11.5 Ophthalmological Evaluations

Visual acuity, Schirmer's tear test, SLIT lamp, Intraocular pressure, Fundoscopy and overall evaluation results will be listed.

### 11.6 Clinical Laboratory Data

All laboratory results will be listed including the test name, result, unit and normal ranges. Supporting clinically significant laboratory results will be flagged.

### 11.7 Vital Signs and ECG

ECG measurements will be listed including the evaluation (Normal/Abnormal, not clinically significant/Abnormal, clinically significant).

All vital signs results will be listed including a flag for clinically notable values for each of the following parameters:

Clinically notable elevated values

- Systolic BP: >=180 mmHg and an increase >=20 mmHg from baseline
- Diastolic BP: >=105 mmHg and an increase >=15 mmHg from baseline.
- Weight: Increase from baseline of 10%
- Heart rate: >=120 bpm with increase from baseline of >=15 bpm
- Temperature: >38 °C

Clinically notable below normal values

- Systolic BP: <=90 mmHg and a decrease >=20 mmHg from baseline
- Diastolic BP: <=50 mmHg and a decrease >=15 mmHg from baseline
- Weight: decrease from baseline of >=10%
- Heart rate: <=50 bpm with decrease from baseline of >=15 bpm
- Temperature: <35 °C

### 11.8 Pregnancy Test

All pregnancy test data will be listed.

## 12. References

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England: 1990). 2009; 45(2):228-247.

2. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008; 26:1148-59.

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# 13. List of Tables/Graphs/Listings

## 13.1 List of Statistical Tables

Not applicable.

## 13.2 List of Graphs

Not applicable.

## 13.3 List of Derived Data Listings

| |
|---|
| **General** |
| Listing 16.02.01.01: Screening Failures |
| Listing 16.02.01.02: Patient Disposition |
| Listing 16.02.01.03: Visits |
| Listing 16.02.01.04: Protocol Deviations |
| Listing 16.02.01.05: Inclusion/Exclusion Summary |
| Listing 16.02.01.06: Demographic and Baseline Disease Characteristics |
| Listing 16.02.01.07: Medical History |
| Listing 16.02.01.08: Subsequent Cancer Therapies |
| Listing 16.02.01.09: Prior and Concomitant Medications |
| **Efficacy Evaluation** |
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| Listing 16.02.02.02: Response Assessments Based on RECIST |
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| Listing 16.02.03.07: Adverse Events Leading to Discontinuation of IMP |
| Listing 16.02.03.08: Non-Serious Grade 2 or Higher Ocular Adverse Events |
| Listing 16.02.03.09: Neuropathy and Skin Assessments |
| Listing 16.02.03.10: Ophthalmological Evaluations |
| Listing 16.02.03.11: Laboratory Results |
| Listing 16.02.03.12: ECG Results |
| Listing 16.02.03.13: Vital Signs |
| Listing 16.02.03.14: Pregnancy Data |

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## 14. Version history

| Version of the SAP and date | Changes |
|---|---|
| Final version 1.0, 3 March 2017 | NA. First final version. |
| Final version 2.0, 16 January 2019 | Updated to reflect changes to the protocol version 3, 4 and 5:<br>- Neuropathy and Skin Assessment<br>- Ophtalmological Evaluations<br>- Non-serious grade 2 or higher ocular events added<br>- Populations removed<br>- 1Q3W schedule kept only<br>Medical history, exposure data and tumor assessments data from the base trials are included.<br>Listings on ECOG performance status and all deaths added.<br>Ocular AE mitigation plan administrations added.<br>Since no prostate cancer patients are enrolled, prostate specific parameters and listings (PSA and Radionuclide bone scan results) are removed.<br>Other minor updates were done to clarify some sections. |