Statistical Analysis Plan

Sponsor:	Genmab A/S
Protocol No:	GEN701
Protocol Version No./ Date:	Version 16.0 / 18 July 2018
Title	First-in-human, dose-escalating safety study of tissue factor specific antibody drug conjugate tisotumab vedotin (HuMax®-TF-ADC) in patients with locally advanced and/or metastatic solid tumors known to express tissue factor
CRF Version No./ Date	5 May 2015 (Dose Escalation Part) 20 Nov 2017 (Cohort Expansion Part)
[redacted] Project Id:	GNMGEN70-GEN701
SAP Version No./ Date:	3.0 / 30 Jul 2019

APPROVALS

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(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Genmab Protocol GEN701. This SAP will cover the analysis of both the Dose Escalation and Cohort Expansion parts of the study.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol Version 16.0 dated 18 July 2018 and eCRFs dated 5 May 2015 (Dose Escalation part) and 20 Nov 2017 (Cohort Expansion part). Any further changes to the protocol or eCRF may necessitate updates to the SAP.

The SAP will be approved prior to programming commencing, and any updated versions of the SAP will be approved prior to database lock.

1.1 CHANGES FROM PROTOCOL

There are no planned changes in analysis from those specified in the protocol.

2. STUDY OBJECTIVES

2.1 PRIMARY STUDY OBJECTIVE

- To establish the tolerability of tisotumab vedotin (HuMax-TF-ADC) in a mixed population of patients with specified solid tumors.

2.2 SECONDARY STUDY OBJECTIVE

- To establish the long term tolerability of tisotumab vedotin (HuMax-TF-ADC) in a mixed population of patients with specified solid tumors.
- To determine the maximum tolerated dose and the recommended dose for phase II studies with tisotumab vedotin (HuMax-TF-ADC).
- To establish the PK profile of tisotumab vedotin (HuMax-TF-ADC) after single and multiple infusions.
- To evaluate the anti-tumor activity of tisotumab vedotin (HuMax-TF-ADC) in a mixed population of patients with specified solid tumors.

3. STUDY DESIGN

This is a dose-escalating, open-label, multicenter phase I/II safety study of tisotumab vedotin (HuMax-TF-ADC) dosed once every 3 weeks in a mixed population of patients with solid tumors known to express tissue factor and where the use of systemically administered tubulin inhibitors is part of standard of care. The study consists of two parts: a Dose Escalation part and Cohort Expansion part. The Dose Escalation part is considered first in human, and the Cohort Expansion part a phase II.

The Dose Escalation part is a standard 3 (+3) design which will evaluate tisotumab vedotin (HuMax-TF-ADC) at doses of 0.30 mg/kg and up (0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.2 and 2.6 mg/kg).

In the absence of unacceptable first cycle toxicities, doses are escalated in the subsequent cohorts, as deemed appropriate by the Data Monitoring Committee (DMC) and confirmed by sponsor. If unacceptable first cycle toxicities are observed, cohorts will be expanded from three to six patients. During the course of the study, the 2.6 mg/kg dose was not used, and an additional cohort with dose of 2.0 mg/kg was used following the 2.2 mg/kg dose cohort.

Patients will be treated for four cycles or until unacceptable toxicity is observed. Patients showing clinical benefit, defined as stable disease (SD) or better, can receive up to a maximum of eight additional treatment cycles (for a maximum of twelve cycles in total, corresponding to 36 weeks).

In the Cohort Expansion part, recruitment will be initiated in five arms encompassing ovary, cervix, endometrium, bladder, and prostate (CRPC). Based on a safety review of data from the first ten patients recruited and followed for at least one cycle (regardless of indication), if the safety profile is deemed safe, the DMC and the sponsor's Safety committee will approve the recruitment of the three remaining arms, esophagus, NSCLC and SCCHN. A minimum of 14 and maximum of 30 patients will be recruited each to the cervix and endometrial indications. In the remaining indications (ovary, bladder, CRPC, NSCLC, esophagus and SCCHN), 14 patients will be recruited.

Cervical and endometrial indications will be expanded from 14 to 30 patients if, and only if, a responder is observed (evaluated after last patient has had four cycles) or, in case of no responders, the DMC evaluates whether it is nevertheless meaningful to expand. If one of these two indications does not appear promising while there is another indication that shows promising efficacy, it may be decided to expand the other indication instead, up to 30 patients. After implementation of Protocol Amendment 13 (Protocol version 14.0), up to 25 additional patients will be recruited to the cervix indication, for a maximum of approximately 55 patients.

Patients will be treated for four cycles with the dose determined from the Dose Escalation part of the study by the DMC and the sponsor's Safety committee. Patients showing clinical benefit, defined as SD or better, can receive up to a maximum of eight additional treatment cycles (for a maximum of twelve cycles in total, corresponding to 36 weeks).

3.1 SAMPLE SIZE CONSIDERATIONS

Up to 217 patients are planned to be enrolled in the study. Taking into account an anticipated screen failure rate of 30%, it is planned that approximately 310 patients are screened for the study.

A maximum of 48 patients are expected in the Dose Escalation part: three to six patients per dose level for eight dose levels. Three patients per dose level, with the possibility to expand to six patients, are considered sufficient to establish the safety basis for escalation to the next dose level.

It is estimated that approximately 169 patients will be enrolled in the Cohort Expansion part (if the ovarian indication continues on to 30 patients and the cervical indication continues on to approximately 55 patients). The information obtained from this number of patients in the Cohort Expansion part is considered enough to provide sufficient basis for the planning and design of further studies.

With the descriptive statistics methodology for the primary endpoint taken into account, the impact of different sample sizes is presented below, showing the probability of making at least one observation of an event with rare incidence:

Probability of rare event	Probability of observation of at least one rare event			
	N=3	N=6	N=112	N=169
10%	27%	47%	>99%	>99%
5%	14%	26%	>99%	>99%
2%	6%	11%	90%	97%
1%	3%	6%	68%	82%
0.1%	0%	1%	11%	16%

Given 112 patients, the probability of making at least one observation of an AE with 2% incidence is 90%. Given 169 patients the probability of making at least one observation of an AE with 1% incidence is 82%. The proposed sample size will give a very good basis for evaluating the safety profile prior to planning further development.

3.2 RANDOMIZATION

No randomization is used for allocation of treatment in this study. Patients are allocated to a single dose level in each cohort.

4. STUDY VARIABLES AND COVARIATES

4.1 PRIMARY VARIABLE

The primary endpoint is the evaluation of AEs: incidences of AEs, serious adverse events [SAEs], infusion-related AEs, CTCAE (Common Toxicity Criteria for Adverse Events) grade ≥ 3 AEs, and AEs related to study drug during the study.

4.2 SECONDARY VARIABLES

- Safety laboratory parameters (hematology, biochemistry, coagulation factors and flow cytometry).
- Skin disorders.
- Bleeding events.
- Neuropathy.
- PK parameters (clearance, volume of distribution and area-under-the-concentration-time curve [$AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$]), maximum concentration [C_{max}], time of C_{max} [T_{max}], pre-dose values (C_{trough}), and half-life of tisotumab vedotin (HuMax-TF-ADC), Total HuMax-TF and free toxin [MMAE]).
- Immunogenicity (ADA) of tisotumab vedotin (HuMax-TF-ADC).

- Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations), change in PSA and CA 125.
- Objective Response (Complete Response [CR] or Partial Response [PR]), Disease Control (CR, PR or SD) after 6, 12, 24 and 36 weeks, Progression-Free Survival (PFS) and Duration of Response.

4.3 EXPLORATORY VARIABLES

- TF expression in tumor biopsies.
- Circulating TF.
- Protein biomarker
  - Circulating cell-free deoxyribonucleic acid (cfDNA)

5. DEFINITIONS

5.1 BASELINE

Unless otherwise stated, Baseline is the last available measurement or assessment prior to first administration of study drug. Assessments on Day 1 of Cycle 1 will be assumed to have been made prior to administration of study drug unless the time indicates that it was after.

5.2 RESPONSE

Response will be assessed from the results of CT-scans at the Screening Visit, and at the end of every second cycle, and any additional CT-scans performed in order to confirm response. Response will be categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) according to the RECIST criteria version 1.1. Patients who died or whose response is not evaluable will be classified as PD. Patients with PR or CR will be classed as responders. No formal confirmation of response is required. However, a repeat CT scan will be performed no less than four weeks (±7 days) after the criteria for response is met to substantiate/confirm CT response. For SD, follow-up measurements must have met the SD criteria at least once and not less than six weeks (± 7 days) after first treatment.

For patients with CRPC, response will be assessed additionally by bone scans which will be done every twelve weeks, and PD is defined as at least 2 new lesions on the bone scan compared to Screening. PD at the first scheduled assessment should be confirmed on a second scan six or more weeks later. Bone scan results will be taken into consideration when assessing whether a patient has PD.

In addition, in the Cohort Expansion parts, response will be assessed by a review committee as well as by the investigator.

Additionally, CA 125 is assessed for patients with ovarian cancer and for patients with endometrial cancer in the Cohort Expansion part. A response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to

CA 125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within two weeks prior to starting treatment.

For patients with CRPC, PSA is assessed. A patient has a response according to PSA if the PSA value has decreased by >50% from baseline. There must be a second measurement between 3 and 4 weeks after the first one to confirm.

In addition, patients will be categorized as either having or not having disease control after 6, 12, 24 and 36 weeks. A patient is defined as having disease control at a specific time point if they have an evaluation of SD, CR or PR at the time point (with a window of ±7 days) or at any time after this.

5.3 BEST OVERALL RESPONSE

The best overall response is the best response recorded while in the trial, using the categories defined in Section 5.2 above. Best overall response will be further categorized as response/non-response where response is CR or PR, and any other category is non-response.

If a patient withdraws with no post-baseline assessment of response, then they will be classed as being a non-responder.

5.4 PROGRESSION FREE SURVIVAL

PFS is defined as the time in weeks from the date of first dose of study medication to PD or death from any cause, whichever comes first. Patients who do not have either event will be censored at the date of the last visit with adequate assessments, or if this is not available, date of first dose of study medication. If a death or progression occurs more than 90 days after the date of the previous visit with an adequate assessment, then they will be censored at the date of the last visit with adequate assessments.

An adequate assessment is defined as an assessment visit with non-missing data in order to assess response and progression corresponding to the indication, and must be prior to the start of any new anti-cancer therapy.

In addition, only deaths that occurred within 90 days of the last visit on the study will be considered when determining whether a patient died for the purposes of analysis of PFS.

Note that undocumented progression is not counted as progression for determining PFS, but a sensitivity analysis in the Cohort Expansion Part will be included counting undocumented progression as progression. Undocumented progression is clinical disease progression recorded by the investigator, but which does not meet the criteria for progression described here.

This is summarized in Table 1: Rules for Progression and Censoring below:

Table 1: Rules for Progression and Censoring

Situation	Date of Progression or Censoring	Outcome
No baseline values	Date of first dose	Censored
Progression documented between scheduled visits	Date of the assessed progression, between visits.	Progressed
No progression	Date of last visit with adequate assessments	Censored

Treatment discontinuation for undocumented progression	Date of last visit with adequate assessments	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessments	Censored
New anti-cancer treatment started	Date of last visit with adequate assessments	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessments visits	Date of death	Progressed
Death or progression more than 90 days after the previous visit with adequate assessments	Date of previous visit with adequate assessments	Censored

In the Cohort Expansion part of the study only, disease progression will also be evaluated by an independent review committee. Further details regarding response and progression assessments will be provided in a separate response evaluation charter. The group performing the response evaluation will follow this charter.

5.5 DURATION OF RESPONSE

Duration of response is defined as the time in weeks from when confirmed response was first documented until the first documented PD, or death from any cause, whichever is earliest. The date used for the date of confirmed response will be the date of assessment for the first assessment where CR or PR was observed and then confirmed at the next assessment. Patients who do not have confirmed response will not have a value for duration of response, and will not be included in the analysis of this variable. Patients with confirmed response who do not subsequently have either disease progression or death from any cause will be censored at the date of the last visit with adequate assessment as defined in Section 5.4 above. For the date to use as event date and censoring date for the end of response, the same rules apply as those for progression free survival given in Section 5.4 above. .

5.6 TREATMENT-EMERGENT ADVERSE EVENTS

Treatment-emergent AEs are defined as those which first occur or increase in severity or relationship to study drug after the first dose of study drug.

For the purposes of determining whether an AE is treatment-emergent or not, and which Cycle it occurs in, any partial or missing dates will be handled as follows. If the date is completely missing, then the AE will be regarded as starting on the date of first study medication. If the year is present, but the month and day are missing, then if the year is before or after the year of first study medication then the day and month will be set to 01Jan, and if it is the same as the year of first study medication then the date will be set to the same as the date of first study medication. If the year and month are present, but the day is missing, then if the month and year are the same as the month and year of the start date of study medication then the date will be set to the same as the start date of study medication, and otherwise the day will be set to 01.

5.7 DURATION OF ADVERSE EVENTS

For the AEs where duration is calculated, it will be calculated as the sum of the duration of individual AEs of that type.

The duration of an individual AE is defined as: (End Date of AE – Start Date of AE)+1. When calculating the sum of the duration of individual AEs, if more than one AE of the same type overlap, then the same day will not be counted twice.

If the AE is ongoing, then the stop date will be taken as the date of last visit, and in the case of incomplete stop dates the following rules will be applied. If the year is present, but the month and day are missing, and the year is the same as the year of the date of last visit, then the date will be set to the date of last visit, otherwise the day and month will be set to 31Dec. If the year and month are present, but the day is missing, then if the month and year are the same as the month and year of the date of last visit, then the date will be set to the date of last visit, otherwise the day will be set to the last day of the month. In the case of the interim analysis during the Cohort Expansion part, if the patient is ongoing in the study at the time of the data cut, then the stop date will be set to the date of the data cut.

5.8 DURATION OF EXPOSURE

Duration of exposure is calculated as:

(Date of last dose of study medication – date of first dose of study medication) + 1

5.9 AGE

Age will be calculated in whole years from the date of birth and the date of signed informed consent.

5.10 TIME SINCE DIAGNOSIS

The time since diagnosis in months will be calculated as:

(Date of Screening Visit – Date of Diagnosis + 1)/30.4

In case of partial dates for the date of diagnosis, missing days will be set to 01 and missing months to Jan.

5.11 STUDY DAY AND CYCLE

Study day will be calculated in relation to the date of first administration of study medication (Day 1). For data on or after the date of the first dose of study medication, the study day is calculated as:

(Date of event/assessment – Date of first dose of study medication) + 1

For data before the day of first dose of study medication, the study day is calculated as:

(Date of event/assessment – Date of first dose of study medication).

When assigning events to cycles, a Cycle will be considered to start at the time of administration of study medication, and continue until the next time of administration of study medication. For the final cycle, this will be considered to end 30 days after the administration of study medication.

5.12 HEIGHT, WEIGHT AND BODY MASS INDEX

Height may be recorded in inches or centimeters. In the tables and listings height will be presented in centimeters, and where recorded in inches will be converted to centimeters using the following conversion factor:

Height in cm = Height in inches x 2.54

Weight may be recorded in pounds and will be converted to kilograms using the following conversion factor:

Weight in kg = Weight in pounds x 0.4536

Body Mass Index (BMI) will be calculated as:

Weight (kg) / (Height $(m)^2$)

6. ANALYSIS SETS

6.1 FULL ANALYSIS SET

The Full Analysis Set 1 (FAS1) is defined as all patients who have been exposed to study drug in the Dose Escalation part of the study. This population will be used for all analyses of data from the Dose Escalation part of the study, with the exception of the PK analysis.

The Full Analysis Set 2 (FAS2) is defined as all patients who have been exposed to study drug in the Cohort Expansion part of the study. This population will be used for all analyses of data from the Cohort Expansion part of the study, with the exception of the PK analysis.

6.2 PHARMACOKINETIC ANALYSIS SET

The PK Analysis Set 1 is defined as all patients who have been exposed to study drug and have at least one PK assessment after the first dose of study medication in the Dose Escalation part of the study. This population will be used for all analyses of PK data from the Dose Escalation part of the study.

The PK Analysis Set 2 is defined as all patients who have been exposed to study drug and have at least one PK assessment after the first dose of study medication in the Cohort Expansion part of the study. This population will be used for all analyses of PK data from the Cohort Expansion part of the study.

7. INTERIM ANALYSES

The analysis of the Dose Escalation part of the study will be done when this part of the study is completed.

The final analysis will be performed when all patients have completed the Cohort Expansion part.

This analysis plan covers both analyses.

During the Dose Escalation part a DMC will review the data from each cohort to determine whether the dose will be escalated, and to determine the dose to be used in the Cohort Expansion

part. An explanation of this process and the dose escalation rules are given in the protocol, and further details will be provided in the DMC charter.

The DMC will also meet to review safety data during the Cohort Expansion part. During the Cohort Expansion part, a pre-planned safety interim review based on cumulative overall safety data is scheduled after the first ten patients (across indications) are followed for at least one cycle. The DMC can propose and the sponsor's Safety committee endorse whether the protocol should continue unchanged, be modified, the dose be reduced, dosing and study entry held for already included patients, additional patients should be included, or whether the study should be discontinued permanently. Based on this interim review, the opening of the remaining three indications (SCCHN, NSCLC and esophageal cancer) can be determined.

A second safety interim is pre-planned during the Cohort Expansion part when 30 patients have been dosed and followed for at least one cycle.

8. DATA REVIEW

8.1 DATA HANDLING AND TRANSFER

[redacted] will be providing the Data management services for this study. Details of the processes followed in order to provide a clean database are specified in the Data Management Plan for the study. This includes details of handling data not stored in the clinical database, such as data from the central laboratory.

8.2 DATA SCREENING

Beyond the data screening built into the [redacted] Data Quality Plan, the [redacted] programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs and extracted from the logs and sent to Data Management for resolution.

Review of a pre-freeze TFL run on clean patients and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFL will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The [redacted] statistician and the sponsor must approve database lock.

9. STATISTICAL METHODS

All analyses will use SAS version 9.4 or higher.

Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be displayed as whole numbers, and will not be displayed for zero counts. Percentages will be calculated from the number of patients with data.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (Std), median, minimum and maximum. The median, minimum and maximum values will be displayed to the same level of precision as the raw data, the mean to a further decimal place and the Std to two additional decimal places, up to a maximum of 4 decimal places.

No formal statistical testing will be done. Where it is specified that confidence intervals will be presented, all confidence intervals will be 95% two-sided confidence intervals.

In the Dose Escalation part, unless otherwise specified, summary statistics will be presented by dose cohort and total.

In the Cohort Expansion part, summary statistics will be presented by cancer type and total.

Unless otherwise stated, all summaries will be produced both for the Dose Escalation part, and for the Cohort Expansion part.

No imputation of missing data is planned, except in the calculation of derived variables as described in Section 5.

Listings of data will be produced separately for the Dose Escalation and Cohort Expansion parts of the study. Listings will be sorted by dose group, patient number and time of assessment (where applicable) for the Dose Escalation part of the study. For the Cohort Expansion part of the study, listings will be sorted by cancer type, patient number and time of assessment (where applicable).

9.1 SUBJECT DISPOSITION

The number and percentage of patients screened, enrolled, and in the Full Analysis Set will be presented, together with the number and percentage of patients who completed four cycles of treatment, withdrew from treatment prematurely and withdrew from the study prematurely. A breakdown of the corresponding reasons for withdrawal from treatment and study will be included in this table.

The number and percentage of patients enrolled at each site will also be tabulated.

In addition, the number and percentage of patients remaining on treatment will also be presented by cycle.

Details of whether patients completed or early terminated from treatment and the study including the reason, and inclusion in the analysis set will be listed for individual patients.

9.2 PROTOCOL DEVIATIONS AND VIOLATIONS

Protocol deviations and violations (PDV) will be entered into the [redacted] Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the PDV data from CTMS, and these will be categorized and PDVs relevant for the analysis identified.

The list of PDVs will be categorized and finalized prior to database lock, and these will be imported into the analysis database for presentation of the significant PDVs in a listing and summary table. Significant PDVs are those indicated as major during medical review.

The categories of PDVs will be documented in a separate document.

A subset of the listed major/significant PDVs deemed to be important by medical review will be presented separately in the body text of the Clinical Study Report.

9.3 TREATMENTS

9.3.1 Extent of Study Drug Exposure

The number of infusions given will be presented in summary tables.

The total duration of exposure in days as defined in Section 5.8 will also be summarized. In addition the duration of infusion in minutes for each cycle will be summarized. Plots showing the duration of infusions and number of infusions will be summarized.

Individual patient data listings of data relating to the infusions, including details of any interruptions, will be provided.

9.3.2 Concomitant Medications

Medications received concomitantly with study drug will be categorized by medication coded term according to WHODRUG dictionary, and in addition coded using the Anatomical Therapeutic Chemical (ATC) classification system. The number and percentage of patients using any concomitant medication will be displayed together with the number and percentage of patients using at least one medication within each medication coded term. The levels of ATC categories to be presented will be level 2 (therapeutic main group), level 3 (therapeutic/pharmacological subgroup) and WHODRUG preferred term.

Medications will be considered concomitant if the stop date is after the first date of study drug or the medication is marked as continuing, and the start date is before the last date of study drug. If there is any doubt as to whether a medication is concomitant due to missing or partial start or stop dates, then the medication will be considered concomitant. Concomitant medications will be listed.

A separate summary table of those medications with a start date on or after the date of last infusion will also be produced.

For the cohort expansion part, a separate summary of the pre-infusion ocular medication at each cycle will be produced, showing the number of patients receiving cooling pads, vasoconstrictor and steroid.

9.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demography data consisting of sex, age, race, ethnicity, height, weight and BMI at the Screening Visit will be summarized.

The number and percentage of patients with each type of cancer (location of primary tumor) will be presented, and time since diagnosis will also be summarized.

Medical history will be coded using the MedDRA dictionary, and summarized by the number and percentage of patients with at least one medical history in each system organ class and preferred term category.

Prior medications will be summarized in a similar manner to concomitant medications. Prior medications will be defined as those with a start date prior to the start date of study drug. Note that medications may be considered both prior and concomitant, and in this case they will be summarized in both tables.

Prior cancer therapies will be coded using WHODRUG and ATC classification and will be summarized by number and percentage of patients receiving any prior cancer therapy by coded term in a similar way to the concomitant medications. In addition, the number of prior lines of therapies will be summarized. In the cohort expansion part, response to the last prior therapy will be summarized. A summary table will be produced of the TNM classification of the disease stage, and in addition the number of patients with distant metastases (number of patients with M classification of '1') will be summarized.

All demographic and baseline characteristics data will be listed. Individual tumor biopsy, peripheral neuropathy history and baseline visual acuity data will also be listed.

9.5 SAFETY ANALYSES

9.5.1 Adverse Events

AEs will be coded using MedDRA. The severity of the AEs will be recorded using the NCI-CTCAE v4.03 grading system. Only treatment-emergent AEs will be included in the summary tables.

An overall summary of treatment-emergent AEs will be presented, including the number of events reported, the number and percentage of patients reporting at least one AE, the number and percentage of patients with at least one SAE, the number and percentage of patients with at least one infusion-related AE, the number and percentage of patients with at least one grade ≥3 AE, the number and percentage of patients with at least one study drug related AE (related or possibly related), the number and percentage of patients discontinuing due to an AE, and the number and percentage of patients who died. In addition, the number of patient days (total number of days in study) will be presented in these tables for each group. This table will also divide AEs into those occurring in Cycle 1 and those occurring any time whilst on treatment (up to the end of the last dose + 30 days).

A breakdown of the number and percentage of patients reporting each AE, and the number of events, categorized by system organ class and preferred term coded according to the MedDRA dictionary, will be presented. Note that for the counts of patients, patients are only counted once within each body system or preferred term.

This summary will be repeated for AEs occurring in Cycle 1, AEs occurring any time on treatment, SAEs, SAEs occurring any time on treatment, infusion-related AEs, grade ≥3 AEs, study drug related AEs (related or possibly related), study drug related grade ≥3 AEs, study drug related SAEs, AEs leading to dose interruption, AEs leading to dose reduction, and AEs leading to discontinuation. AEs occurring any time on treatment are those with an onset date on or before the date of last dose + 30 days.

Further summary tables will be produced by system organ class and preferred term, additionally split by NCI-CTC grade and relationship. This will be done for all AEs, all SAEs, and AEs in Cycle 1.

AEs of special interest will be defined as AEs of skin rash, bleeding, neuropathy, neutropenia, neutropenic fever, anemia, thrombocytopenia, vomiting, diarrhea and infusion-related AEs. These will be identified as described in Table 2 below, where PT=Preferred Term, and

HLT=High Level Term. A separate document, an excel spreadsheet called SMQs for GEN701 containing a tab for different types of AE of special interest, is referred to in the table below and is an appendix to this SAP.

Table 2: List of AEs of Special Interest

Skin Rash	PT: Drug eruption, Lip ulceration, Rash, Rash maculo-papular, Rash pustular
Bleeding	Refer to list of terms in Haemorrhage tab of SMQ appendix.
Neuropathy	Refer to list of terms in peripheral neuropathy tab of SMQ appendix.
Neutropenia	PT: Neutrophil count abnormal PT: Neutrophil count decreased PT: Neutrophil percentage abnormal PT: Neutrophil percentage decreased PT: Band neutrophil count decreased PT: Band neutrophil percentage decreased HLT: Neutropenias
Neutropenic fever	PT: Febrile neutropenia
Anemia	PT: Anaemia PT: Hemorrhagic anaemia PT: Anaemia of chronic disease PT: Anaemia of malignant disease PT: Aplastic anaemia PT: Hypoplastic anaemia

Thrombocytopenia	PT: Platelet count abnormal PT: Platelet count decreased PT: Thrombocytopenia PT: Thrombocytopenic purpura PT: Thrombotic Thrombocytopenic purpura
Vomiting	PT: Vomiting
Diarrhea	PT: diarrhea PT: diarrhea hemorrhagic
Infusion Related Reaction (IRR)	Any AE with onset date and time between start date and time of infusion and end time of infusion plus 24 hours, considered related by the investigator, and with preferred term of Arthralgia, Asthenia, Bronchospasm, Chills, Cough, Hyperhidrosis, Dizziness, Pyrexia, Fatigue, Flushing, Headache, Hypertension, Hypotension, Infusion related reaction, Lethargy, Malaise, Myalgia, Nausea, Pruritus, Tachycardia, Tumor pain, or high level term of 'Exfoliative conditions', 'Dyspneas', 'Dyspnoeas' or 'Breathing abnormalities' or high level group term of 'Allergic conditions'.
Conjunctival disorders	Refer to list of terms in Conjunctival disorders tab of SMQ appendix.
Corneal disorders	Refer to list of terms in Corneal disorders tab of SMQ appendix.
Scleral disorders	Refer to list of terms in Scleral disorders tab of SMQ appendix.
Retinal disorders	Refer to list of terms in Retinal disorders tab of SMQ appendix.
Peri orbital and eyelid disorders	Refer to list of terms in Peri orbital and eyelid disorders tab of SMQ appendix.
Ocular infections	Refer to list of terms in Ocular infections tab of SMQ appendix.
Optic nerve disorders	Refer to list of terms in Optic nerve disorders tab of SMQ appendix.
Any ocular event	This is any AE in any of the 7 ocular categories above – conjunctival disorders, corneal disorders, scleral disorders, retinal disorders, peri orbital and eyelid disorders, ocular infections, and optic nerve disorders.

The number and percentage of patients with AEs in each category will be summarized, and a separate summary of AEs of special interest broken down by category and preferred term will be provided. Separate tables will be produced for all AEs of special interest, for AEs of special interest occurring in Cycle 1, AEs of special interest which are serious, and AEs of special interest occurring in Cycle 1 which are serious. For each of these groups of AEs, a further summary table will be produced broken down by maximum NCI-CTCAE grade. Finally, a summary of the duration of the AEs will be presented separately for skin rash AEs, bleeding AEs and neuropathy AEs. The summary of duration of the AEs will present the number of AEs of that type, and summary statistics for the duration in days of the individual events.

For skin rash, bleeding and neuropathy AEs, plots showing the onset day, duration and intensity (NCI-CTCAE grade) of individual AEs will be produced. A separate plot will be produced for each type of AE and each cohort in the Dose Escalation part, and each cancer type in the Cohort Expansion part. For the bleeding events, separate plots will be produced for minor bleedings, major bleedings and all bleedings.

In the Cohort Expansion part, the ocular events (defined as those in the Any ocular event category above) will be additionally be summarized by whether the patient entered the study prior to the mitigation plan (first dose of study medication <= 22Dec2016), or after the mitigation plan (first dose of study medication > 22Dec2016). This will be done for all patients overall, and then repeated for each cancer type.

A further figure will be produced which is a bar graph of all adverse events by cycle and dose cohort in the Dose Escalation part, and cancer type in the Cohort Expansion part, showing the percentage of patients with an AE. This will be further split by maximum CTCAE grade.

All AEs (including non-treatment-emergent events) recorded in the eCRF will be listed. Separate listings of SAEs, AEs leading to death, AEs leading to discontinuation, AEs with CTCAE grade≥3, AEs leading to dose interruption, AEs leading to dose reduction, study treatment related AEs, AEs occurring in Cycle 1 and AEs of special interest will be produced. In the Cohort Expansion part, a listing of AEs with CTCAE grade>=3 will be produced for those patients determined to have a positive ADA result only.

Where the NCI-CTCAE grade of an AE is missing, it will be assumed to be ≥3, and where the relationship is missing it will be assumed to be related.

9.5.2 Laboratory Data

9.5.2.1 HEMATOLOGY, BIOCHEMISTRY AND COAGULATION FACTORS

Hematology, biochemistry and coagulation factors will be analyzed at the site laboratory and results recorded on the eCRF in the Dose Escalation part of the study. In the Cohort Expansion part, these will be tested centrally and the data transferred from the vendor. Values will be presented in SI units, and where values are recorded in different units in the eCRF, they will be converted into SI units prior to the data being summarized and listed.

The following parameters are assessed:

Hematology: Red Blood Cell Count; Hemoglobin; Hematocrit; Mean Corpuscular Hemoglobin; Mean Corpuscular Hemoglobin Concentration; White Blood Cell Count; Neutrophils, Absolute; Neutrophils, Percent; Lymphocytes, Absolute; Lymphocytes, Percent; Monocytes, Absolute; Monocytes, Percent; Eosinophils, Absolute; Eosinophils, Percent; Basophils, Absolute; Basophils, Percent; Reticulocytes; Platelet Count

Biochemistry: Sodium, Potassium, Calcium, Magnesium, Creatinine, Blood Urea Nitrogen , AST, ALT, Alkaline Phosphatase, Albumin, Glucose, Total Creatine Kinase, Total Bilirubin, lactate dehydrogenase, Uric Acid, S-Ferritin, C-Reactive Protein, Glycosylated Hemoglobin.

Coagulation Factors: Prothrombin time, INR, aPTT, D-dimer, Fibrinogen.

Summaries of the actual values at baseline and percentage change from baseline at each post-baseline visit and will be presented at each visit where they are assessed.

Laboratory values will be assigned an NCI-CTC grade according to the NCI-CTCAE v4.03 grading system. The following parameters will be assigned grades:

Hematology: Hemoglobin; White Blood Cell Count; Lymphocytes, Absolute; Neutrophils, Absolute: Platelets.

Biochemistry: Albumin, Alkaline Phosphatase, ALT, AST, Total Bilirubin, Calcium, Glucose, Magnesium, Potassium, Sodium.

Coagulation Factors: Fibrinogen, INR, aPTT.

For the other parameters, it is not possible to assign an NCI-CTC grade.

For parameters where an NCI-CTC grade is defined, a grade will be assigned for each result, and the maximum post-baseline grade and shift from baseline will be summarized.

Unscheduled assessments will be included in the summary statistics when looking across the study as a whole.

Reference ranges from the individual laboratories will be used, and no transformation of the results to a single normal range will be applied.

All laboratory data will be listed, which will include the NCI-CTC grade and investigator's assessment of clinical significance, and in addition a separate listing of Grade ≥3 results will be produced.

Plots of mean laboratory values over time and values for individual patients over time will be presented by dose group for the Dose Escalation part and by cancer type for the Cohort Expansion part for each parameter.

Any additional laboratory assessments taken as a result of the bleeding or neuropathy assessment will be listed separately.

Pregnancy test results will also be listed.

9.5.2.2 FLOW CYTOMETRY

Peripheral blood samples for assessment by flow cytometry will be collected at Day 1 of Cycle 1 and Cycle 5 and at the End of Study Visit. The following will be measured:

Total T-cells ($CD3^+$), Helper T-cells ($CD3^+CD4^+$), Cytotoxic T-cells ($CD3^+CD8^+$), NK-cells ($CD3^-CD56^+CD16^+$) and B-cells ($CD45^+CD19^+$).

Descriptive statistical summaries of each cellular population (percentages and absolute cell counts) at each visit will be tabulated for each cohort. The median percentage change from Cycle 1 Day 1 (baseline) at Cycle5 day 1 and EOS visits will be presented for each cohort. In addition in the Cohort Expansion part, summaries of each cellular population at Cycle1 Day1 and the percentage change in each cellular population from Cycle 1 Day 1 to Cycle 5 Day 1 will be presented by overall response (PD,SD, PR, CR) rather than cancer type.

9.5.2.3 SEROLOGY

For the parameters of HBsAG, Anti-HBs, Anti-HBc, Hepatitis C, CMV IgG, CMV IgM, and HPV (for patients with squamous cell carcinoma of the head and neck or cervical cancer only) samples will be collected at the Screening and End of Study visits, and analyzed at a central laboratory. The results of positive/negative for each parameter for each patient will be listed, and the number and percentage of patients with shifts from negative to positive at any time post-baseline will be summarized.

9.5.2.4 BIOMARKERS

Tissue Factor (TF) expression will be measured by immunohistochemistry (IHC) assay in tumor biopsy samples provided at baseline (screening). TF expression will be reported as cellular membrane staining by H-score, which is a composite scoring of the positive TF staining within the tissue sample. The score is obtained by the formula: 3 x percentage of strongly staining cells + 2 x percentage of moderately staining cells + percentage of weakly staining cells, giving a range of 0 to 300. Descriptive summary statistics will be provided for TF expression (number of patients with biopsies with TF results, mean, median, minimum, maximum, std) at baseline for all patients in dose escalation, and by indication in the expansion phase. In addition, summaries of TF expression (membrane H Score) at baseline will be provided by overall response (PD, SD, PR, CR) for each indication in the expansion phase. Finally, summaries of TF expression (membrane H Score) at baseline will be provided for patients with overall response of SD, PR or CR) versus progressive disease (PD) in each indication.

Circulating tissue factor will be measured from samples taken at Screening and Day 1 of Cycle 5 in the Dose Escalation part, and at Screening and Day 15 of Cycle 4 in the Cohort Expansion part. Descriptive summary statistics (mean, median, max, min, std) of cTF values at each visit and changes from screening will be provided per dose cohort in dose escalation and in the expansion phase. In the expansion phase, this summary will be repeated by subgroup for patients with overall response of SD, PR or CR, and patients with overall response of PD. For the expansion phase cohorts, median changes in cTF (Cycle 4 Day 15 vs Screening) will be plotted per indication. Median change in cTF (Cycle 4 Day 15 vs Screening) in patients with overall response of SD, PR or CR and those with progressive disease (PD) will also be plotted per cohort, for all the expansion cohorts. Association between cTF and TF expression by IHC (H-score) will be assessed by plotting change in cTF versus baseline H-score.

Cell free DNA (cfDNA) will be measured from samples taken at Screening and Cycle 5 Day 1 in the Dose Escalation, and at Screening and Cycle 4 Day 15 in the Cohort Expansion phase.

Descriptive summary statistics (mean, median, max, min, std) of cfDNA values at each visit and changes from screening will be provided per dose cohort in dose escalation and in the expansion phase. In the expansion phase, this summary will be repeated by subgroup for patients with overall response of SD, PR or CR, and patients with overall response of PD. For the expansion phase cohorts, median changes in cfDNA (Cycle 4 Day 15 vs Screening) will be plotted per indication. Median change in cfDNA (Cycle 4 Day 15 vs Screening) in patients with overall response of SD, PR or CR, and patients with progressive disease (PD) will also be plotted per cohort, for all the expansion cohorts.

9.5.3 Skin Disorders

The number and percentage of patients with skin rash and the number of individual occurrences of skin rashes at any time will be summarized.

This will be broken down by the maximum percentage of body surface area affected (<10%, ≥10-30%, and >30%) and whether there are any vesicles.

The detailed information on skin rashes assessed will be listed individually for each patient.

9.5.4 Bleeding Assessment

The number and percentage of patients with bleeding events and the number of individual occurrences of bleeding events at any time will be summarized. This will be repeated for major bleeding events.

A listing presenting the additional detailed information collected on bleeding events including location, suspected cause and intensity by individual patient will be produced.

In addition, summary tables and bar charts will be produced showing the percentage of patients with bleeding in each location. A patient may be included in more than one category, as a patient may have bleeding in more than one location. The summary table and bar chart will be presented for all patients overall and by dose level for the Dose Escalation part of the study, and cancer type for the Cohort Expansion part. There will also be separate tables and bar charts for bleeding with onset during Cycle 1.

9.5.5 Peripheral Neuropathy

An assessment of neuropathy will be done at every visit. The number and percentage of patients with neuropathy at any time will be summarized. This will be done for all neuropathy overall, and then repeated for motor, sensory and autonomic neuropathy separately.

Details of the results of the neuropathy exam including type (polyneuropathy, mononeuropathy or other), symptoms and cause of the neuropathy will be listed for each individual patient.

9.5.6 Ophthalmology

In the Cohort Expansion part, Individual patient data from the ophthalmology assessments will be listed. This includes visual acuity, Schirmer's tear test, SLIT lamp, interocular pressure, fundoscopy, overall evaluation, and treatment initiated/adjusted. Summaries of visual acuity, Schirmer's tear test, SLIT lamp (hyperemia, conjunctival staining and cornea staining) and intraocular pressure and fundoscopy will be produced.

9.5.7 Other Safety Assessments

9.5.7.1 VITAL SIGNS

Vitals signs of temperature, blood pressure and heart rate will be assessed at each visit.

Summaries of the actual values at each time point and change from baseline at each post-baseline time point will be presented at each scheduled time point where they are assessed.

A listing of the vital signs data by patient will be produced, including the change from baseline value. Weight will be included in the listing at the visits where it is measured.

In addition, a separate listing of patients with abnormal vital signs values at any time will be produced, where an abnormal value is systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, heart rate of <60 bpm or >100 bpm, or temperature of >37.5°C.

9.5.7.2 ECG

ECG data of HR, PR, QRS, QTcB and QTcF obtained from the central reading, and the investigator's judgment of whether clinically significant, will be collected at Screening and three times on Day 1 of each Cycle.

Summaries of the actual values at each visit and change from baseline at each post-baseline visit will be presented at each scheduled visit where they are assessed for the numerical ECG parameters. Where multiple assessments are done at the same visit, the average of the values at that visit will be used for the calculation of the summary statistics. For calculating baseline value, if multiple assessments were taken on the same date as the last measurement prior to IMP administration, then the average of all values on that date prior to IMP administration will be used as the baseline value.

All ECG results will be listed, and a separate listing of ECG data for patients who have a clinically significant result at any time, as indicated by the investigator, will be provided.

9.5.7.3 PHYSICAL EXAMINATION

Physical examination data will be collected at Screening, Day 1 of Cycle 1 and 2 and End of Study. Listings of individual physical examination data will be provided for each patient.

A separate listing of changes from Normal at Screening to Abnormal at any time post-baseline, or from Abnormal – not clinically significant at Screening to Abnormal – clinically significant at any time post-baseline will be produced.

9.5.7.4 ECOG

ECOG data will be collected at Screening, Day 1 of each cycle, and at the End of Study Visit. These data will be listed for each patient, and the number and percentage of subjects in each category summarized.

9.6 PHARMACOKINETIC ANALYSES

9.6.1 Pharmacokinetic Concentrations

Blood samples for assessment of HuMax-TF-ADC, total HuMax-TF (conjugated and non-conjugated) and MMAE will be drawn for central analysis in accordance to the timing provided in the tables below.

Table 3: PK Sampling in the Dose Escalation Part

Treatment Cycle	**Screening**	**Cycle 1-2**						**Cycle 3-4**			**Cycle 5-12**			**Follow-Up**	**Unscheduled**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**1**	**2**	**3**	**1-4**	**1-X**
Day/Week	-	1d	2d	4d	8d	11d	15d	1d	8d	15d	1d	8d	15d	6 weekly	
Before Infusion *(on infusion days)*	X	X	X[1]		X		X	X			X			X	X[3]
End of infusion *(+15 minutes)* [2]		X						X			X				
+ 2 hours *(± 15 minutes)* after end of infusion [2]		X													
+ 5 hours *(± 30 minutes)* after end of infusion [2]		X													
+ 12 hours *(± 60 minutes)* after end of infusion [2]		X													

[1] *Time window for the Day 2 sampling in the Dose Escalation Part is 24 hours ± 2 hours after end of infusion on Day 1.*

[2] *Allowed time windows are indicated in parentheses.*

[3] *Optional.*

Table 4: PK Sampling in the Cohort Expansion Part

Treatment Cycle	**Screening**	**Cycle 1-2**			**Cycle 3-4**			**Cycle 5-12**			**Follow-Up**	**Unscheduled**
Visit Number	**0**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1-4**	**1-X**
Day/Week	-	1d	8d	15d	1d	8d	15d	1d	8d	15d	6 weekly	
Before Infusion *(on infusion days)*	X	X	X	X	X			X			X	X[2]
End of infusion *(+15 minutes)* [1]		X			X			X				
+ 2 hours *(± 15 minutes)* after end of infusion [1]		X										

[1] *Allowed time windows are indicated in parentheses.*

[2] *Optional.*

The assay to detect Humax-TF-ADC is GNM124EL-131243-A_PK(IgG1 specific), and the assay to detect Total Humax-TF is GNM124EL-131243-B_PK(MMAE specific).

Plasma concentrations will be summarized for HuMax-TF-ADC, total HuMax-TF and MMAE. Concentrations below the lower limit of quantitation (LLOQ) will be set to ½LLOQ in the computation of all summary statistics for plasma concentrations.

Descriptive statistics (number of patients, mean, geometric mean, Std, geometric CV, median, minimum, and maximum) will be used to summarize the plasma concentrations within a cohort by scheduled time.

The geometric CV is defined as:

Geometric CV = $\sqrt{(\exp[\sigma^2] - 1)}$

where σ^2 is the variance of the log transformed values.

Linear and semi-logarithmic plots of the mean plasma concentration by scheduled sampling time and individual plasma concentration by scheduled sampling time will be provided for HuMax-TF-ADC, total HuMax-TF and MMAE. These plots will show time in days post dose and concentrations in ug/mL for HuMax-TFADC and total Humax-TF and ng/ml for MMAE. In these plots the values below LLOQ values will be set to 1/2 LLOQ. In the Dose Escalation part, these plots will be produced separately for cycle 1 and Cycle 2. Linear plots of mean trough level with standard deviations will be presented to assess attainment of steady state for HuMax-TF-ADC, total HuMax-TF and MMAE for expansion cohort.

All individual patient plasma concentration data will be listed.

9.6.2 Pharmacokinetic Parameters

PK parameters for HuMax-TF-ADC, total HuMax-TF and free toxin (MMAE) will be estimated using noncompartmental methods with Phoenix WinNonlin® (WNL) Version 6.3 or higher (Pharsight Corp., Mountain View, CA). PK computations may also be performed in SAS® Version 9.1 or higher.

The plasma PK parameters will be estimated from the concentration-time profiles for all PK population patients. For the calculation of PK parameters, pre-dose concentration <LLOQ and concentration prior to the first quantifiable concentration that are <LLOQ should be set to 0.00. An observation that is <LLOQ which occurs between measurable observations should be set to "missing" for the purposes of calculating the PK parameters. If there are more than 2 consecutive <LLOQ concentrations after C_{max} , then all concentrations after that may be treated as missing after review of available documentation (eg, bioanalytical report, clinical report) by the project pharmacokineticist in consultation with the sponsor. Actual sampling times will be used in all computations involving sampling times.

Descriptive statistics (number of patients, mean, geometric mean, Std, geometric CV, median, minimum, and maximum) will be used to summarize all the relevant PK parameters within cohort by dose group.

For cycles 1 and 2, the following PK parameters will be calculated based on non-compartmental (NCA) methods:

Parameter	Description	SAS Programming Notes
C_{max}	Maximum observed plasma concentration. Observed peak concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL
T_{max}	Time to maximum observed plasma concentration. First observed time to reach peak concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL
AUCs	Calculated by the linear trapezoidal rule, expressed in units of concentration x time.	
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable concentration. Calculated as $\Sigma[(ci + ci\text{-}1)(ti - ti\text{-}1)/2]$, where ci is the concentration of the ith sample (i=2 to n), ti is the time of the ith serum sample, and n is the number of nonmissing samples at 0 to t hours.	AUClast from WNL
$AUC_{0-\infty}$ [Dose Escalation part only]	Area under the plasma concentration-time curve from time zero extrapolated to infinity. Calculated as $AUC0\text{-}inf = AUC0\text{-}t + Clast/\lambda z$, where Clast is the last measurable analyte concentration and λz is the terminal elimination rate constant, expressed in inverted units of time.	AUCINF_obs from WNL If Rsq ≤ .80 or AUC_%Extrap_obs >20% then parameter is deleted
$t_{1/2}$ [Dose Escalation part only]	Half-life, expressed in time units. Calculated as $\ln(2)/\lambda z$, expressed in time units. Linear regression of at least 3 points in the terminal phase and coefficient of determination r^2 greater than 0.80 is required to retain $t_{1/2}$.	HL_Lambda_z from WNL If Rsq ≤ .80 then parameter is deleted

Parameter	Description	SAS Programming Notes
CL [Dose Escalation part only]	Total clearance (IV), expressed in volume / time unit. Calculated as: CL = Dose (iv)/AUC0-inf	Cl_obs from WNL If Rsq ≤ .80 or AUC_%Extrap_obs >20% then parameter is deleted
Vz [Dose Escalation part only]	Volume of distribution of the terminal phase after iv administration, expressed as volume Calculated as Vz = Dose (iv)/(AUC0-inf * λz)	Vz_obs If Rsq ≤ .80 or AUC_%Extrap_obs >20% then parameter is deleted

In the derivation of CL and Vz for the total HuMax-TF, the dose will be assumed to be 97% of the total dose. CL and Vz will not be calculated for MMAE.

Over the entire study period (first to last cycle), C_{trough} will be tabulated, where C_{trough} is defined as pre-dose plasma concentration values on Day 1 of Cycles 1-12.

All PK parameters will be calculated separately for Cycle 1 and Cycle 2If deemed applicable compartmental modeling approaches to parameter estimation will be applied. Further exploratory analyses of PK data may be performed.

9.6.3 Statistical Analysis of Pharmacokinetic Data

For the Dose Escalation part, dose proportionality of Cycle 1 C_{max} ,Cycle 1 AUC_{0-t} and Cycle 1 AUC_{inf} will be assessed using the power model for all 3 analytes. The power model assumes a linear relationship between the natural log transformed parameter and the natural log transformed dose. Dose proportionality will be assessed by estimating mean slope with the corresponding two-sided 90% confidence interval (CI) from the power model. The estimate and 90% confidence interval for the slope will be presented.

The relation between derived PK parameters and covariates such as actual dose will be evaluated graphically for the Dose Escalation part. This will be done by plotting estimates of Cmax, AUC_{0-t} and AUC_{inf} from the analysis described above log dose for cycle 1.

9.7 IMMUNOGENICITY

Blood samples will be taken for analysis of ADA at Screening, Day 1 (pre-dose) of each cycle, and at the End of Study Visit, and results will be obtained as positive or negative. Confirmed positive results will be determined.

Summary tables presenting number and percentage of patients with confirmed positive results at each visit and a confirmed positive result any time post-baseline will be presented. In addition, individual patient data listings will be produced of the ADA results. An additional listing of ADA results matched with the pre-dose PK samples on the same date will be produced. Values will be flagged if Humax-TF-ADC is > 50 µg/ml, Total Humax-TF > 50 µg/ml, or MMAE > 2µg/ml.

For the purposes of the tables and listings by ADA, a patient will be considered ADA positive if they have at least one post-baseline confirmed ADA positive sample.

9.8 EFFICACY ANALYSIS

All individual scan data, PSA and CA125 values, and all derived efficacy variables will be listed for each patient.

9.8.1 Response

Best Overall Response will be evaluated and summarized. Number and percentage of patients in each category and who are responders/non-responders will be presented, together with a 95% confidence interval calculated using the Clopper-Pearson exact method. We will also repeat this table but requiring confirmation for PR and CR.

For the Cohort Expansion part this summary will also be repeated by response to last prior therapy, and number of prior lines of therapy (0-1, 2-3 and >=4).

In addition, the number and percentage of patients with and without disease control after 6, 12, 24 and 36 weeks and associated confidence interval calculated using the Clopper-Pearson exact methods will be provided.

These summaries will be presented by indication as well as by dose cohort.

A separate summary of bone scan data for the subjects with CRPC where this is done will present the number and percentage of patients with No new lesions and New Lesions at each assessment.

In the Cohort Expansion part, a swimlane plot showing the overall response at each assessment will be produced.

In the Cohort Expansion part, response will be assessed both by the investigator, and also by an independent review committee, and separate summaries and listings will be provided for both assessments.

For the Cohort Expansion part, a separate summary of the best overall response by whether the patient had an ADA result that was determined to be positive rather than cancer type will be produced. This will be done for both the investigator assessment and the independent review committee assessment.

In addition, for patients with ovarian cancer and those with endometrial cancer in the Cohort Expansion part, response according to CA 125 will be assessed, and this will be summarized as the number and percentage of patients with a response.

Finally, for patients with CRPC, response according to PSA will be assessed, and this will also be summarized as the number and percentage of patients with a response.

9.8.2 Progression Free Survival

The proportion of patients with PFS will be summarized using Kaplan-Meier estimates and 95% confidence intervals at 12, 24, 36, 48 and 60 weeks. The number and percentage of patients experiencing PD or death and the number and percentage of patients who are censored will also be presented. In addition, the Kaplan-Meier estimate for the median PFS together with a 95%

confidence interval will be provided. The associated Kaplan-Meier plots will be produced to display the results graphically for all dose groups combined in the Dose Escalation part, and for each cancer type and total in the Cohort Expansion part.

In the Cohort Expansion part, PFS will be derived based on the investigator's assessments, based on investigator's assessments including undocumented progression as disease progression, and also based on the assessments of the independent review committee. Separate summaries and listings will be provided for all three assessments.

9.8.3 Duration of Response

Kaplan-Meier estimates and 95% confidence intervals for duration of response will be presented at 12, 24, 36, 48 and 60 weeks. The number and percentage of patients whose response ends, and who are still responding (censored) will be presented. The Kaplan-Meier estimate for the median duration of response and 95% confidence interval will be provided. The associated Kaplan-Meier plots will be produced to display the results graphically for all dose groups combined in the Dose Escalation part, and for each cancer type and total in the Cohort Expansion part.

In the Cohort Expansion part, duration of response will be derived based on the investigator's assessments, and also based on the assessments of the independent review committee, and separate summaries and listings will be provided for both assessments.

9.8.4 Tumor Shrinkage

The maximum change from baseline in the sum of the target lesion measurements at any time on study will be included in the listings and plotted using waterfall plots. The percent change will be plotted in addition to the absolute change.

In the Cohort Expansion part only, the change from baseline in the sum of the target lesion measurements from the CT-scan evaluation at the end of four cycles and at the end of treatment will be summarized.

9.8.5 PSA and CA 125

Summary statistics of PSA and CA 125 and actual and percentage change from baseline will be presented by cycle, and in addition plots of individual patient data over time (actual values and percent change from baseline) will be produced for these parameters. In the Cohort Expansion part, plots of mean and median by cancer type over time will also be produced. Note that PSA is assessed for subjects with CRPC only, and CA 125 is measured for subjects with ovarian cancer only, and in addition patients with endometrial cancer in the Cohort Expansion part.

10. VALIDATION

[redacted]s goal is to ensure that each TFL delivery is submitted to the highest level of quality. [redacted] quality control procedures will be documented separately in the study specific quality control plan.

11. REFERENCES

The NCI-CTCAE v4.03 criteria can be found here:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

This will be used for assigning Grades to laboratory parameters.

APPENDIX 1 GLOSSARY OF ABBREVIATIONS

Glossary of Abbreviations:	
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ATC	Anatomical Therapeutic Chemical
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BMI	Body mass index
cfDNA	Circulating cell-free deoxyribonucleic acid
CMV	Cytomegalovirus
CR	Complete Response
CRPC	Castration-resistant prostate cancer
CT	Computerized tomography
CTCAE	Common Toxicity Criteria for Adverse Events
cTF	Circulating Tissue Factor
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen

HPV	Human papilloma virus
HuMax®-TF-ADC	HuMax Tissue Factor antibody drug conjugate
INR	International normalized ratio
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PD	Progressive disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PSA	Prostate specific antigen
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable Disease
Std	Standard deviation
TF	Tissue Factor
WHO	World Health Organization

APPENDIX 2 LIST OF IN-TEXT TABLES, FIGURES, AND LISTINGS

Not applicable

APPENDIX 3 LIST OF POST-TEXT TABLES, FIGURES, LISTINGS, AND SUPPORTIVE SAS OUTPUT APPENDICES

List of Post-Text Tables, Figures, Listings, and Supportive SAS Output Appendices:		
Output	**Title 1**	**Title 2**
TABLES **Dose Escalation Part**		
Table 14.1.1.1-A	Patient Disposition by Dose Cohort	Dose Escalation Part (All Enrolled Patients)
Table 14.1.1.2-A	Enrollment by Center and Dose Cohort	Dose Escalation Part (All Enrolled Patients)
Table 14.1.1.3-A	Significant Protocol Deviations by Dose Cohort	Dose Escalation Part (All Enrolled Patients)
Table 14.1.1.4-A	Patients Remaining on Treatment by Cycle and Dose Cohort	Dose Escalation Part (All Enrolled Patients)
Table 14.1.2.1-A	Demographic Characteristics by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
Table 14.1.3.1-A	Medical History by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
Table 14.1.3.2-A	History of Cancer by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
Table 14.1.3.3-A	Disease Stage by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
Table 14.1.3.4-A	Summary of Membrane H-Score by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
Table 14.1.4.1-A	Prior Medications by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
Table 14.1.4.2-A	Prior Cancer Therapies by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
Table 14.1.4.3-A	Number of Prior Lines of Cancer Therapies by Dose Cohort	Dose Escalation Part (Full Analysis Set 1)
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Appendix 16.1.9.4-B	Kaplan-Meier Analysis of Duration of Response (Investigator Assessment)	Cohort Expansion Part (Full Analysis Set 2)
Appendix 16.1.9.5-B	Kaplan-Meier Analysis of Duration of Response (Review committee Assessment)	Cohort Expansion Part (Full Analysis Set 2)

APPENDIX 4 SHELLS FOR IN-TEXT TABLES, FIGURES, AND LISTINGS

Not applicable

APPENDIX 5 SHELLS FOR POST-TEXT TABLES, FIGURES, AND LISTINGS

Shells for post-text Tables, Figures and Listings are contained in a separate document.