Statistical Analysis Plan

Sponsor:	Genmab A/S
Protocol No:	GEN702 – Cohort Expansion part
Version No./Date	Final 5.0 (incorporating Protocol Amendment 4), 06 Jul 2017
Title	DOSE-ESCALATING AND COHORT EXPANSION SAFETY TRIAL 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
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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Genmab Protocol GEN702 for the Cohort Expansion part of the trial. (Note: the statistical methods for the GEN702 Dose Escalation part are described in a separate SAP dated 13 Nov 2015).

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 dated 06JUL2017 and eCRF dated 07SEP2017. 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

The protocol planned for two or three cancer type arms. Patients with cervical or ovarian cancer were selected for the trial. Since the assessments for prostate specific antigen (PSA) were planned for patients with prostate cancer only, no PSA summaries or listings will be provided.

The protocol states that an additional interim analysis may be performed when 20 patients have completed four cycles (or have been withdrawn earlier), however this was not done.

2.0 Study Objectives

2.1 Primary Study Objective

To establish the tolerability of tisotumab vedotin (HuMax® tissue factor antibody drug conjugate [HuMax-TF-ADC]) dosed 3 times every 4 weeks (3q4wk) in a mixed population of patients with specified solid tumors.

2.2 Secondary Study Objective

- To determine the maximum tolerated dose (MTD) and the recommended dose for phase II trials (RP2D) with tisotumab vedotin (HuMax TF-ADC) dosed 3q4wk.
- To establish the pharmacokinetic (PK) profile of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk.
- To evaluate the anti-tumor activity of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk in a mixed population of patients with specified solid tumors.

Trial objectives remain unchanged despite the protocol updates related to implementation of the urgent safety measure (Protocol Amendment 4.0).
The objective to determine the MTD and RP2D applied to the Dose Escalation part of the study.

3.0 Study Design

This is a phase I/II open-label, dose escalating and cohort expansion, safety trial of tisotumab vedotin (HuMax TF-ADC) dosed 3q4wk (Days 1, 8 and 15 of each 28-day cycle) in a mixed patient population with solid tumors to establish the safety profile.

The trial consists of two parts: A Dose Escalation part followed by a Cohort Expansion part. The Dose Escalation part is a phase I trial and the Cohort Expansion part is a phase II trial.

The Dose Escalation part had a standard 3 (+3) design. In each dose cohort, the initial three patients must include at least two different cancer types. Three dose levels are anticipated, with three to six patients per dose level, plus a potential intermediate dose cohort.

There were two dose cohorts (0.9mg/kg and 1.2 mg/kg) in the dose Escalation part and the RP2D was 1.2 mg/kg 3q4wk.

The Cohort Expansion part will have a parallel group design; 20 to 30 patients are planned to be enrolled in two or three indication arms, including cervical and ovarian. Patients in the Cohort Expansion part will be treated with the RP2D from the Dose Escalation part. Tisotumab vedotin (HuMax-TF-ADC) will be administered on Day 1, 8 and 15 of a 28-day cycle. Patients may be treated for up to 9 cycles

The treatment period will last for up to 36 weeks or until unacceptable toxicity or disease progression at the discretion of the treating physician. Reduced dose can be administered in accordance with the mitigation strategies or at the discretion of the treating physician based on individual patient observed toxicity profile and quality of life evaluation, and after consultation and agreement by the sponsor Medical Officer.

The trial will be stopped when the last patient enrolled in the Cohort Expansion part completes the trial or when the last ongoing patient has discontinued treatment and attended the Safety Follow-up Visit, whichever occurs first.

Severe ocular toxicity has been observed at 1.2 mg/kg 3q4wk (the RP2D for the Cohort Expansion part). After implementation of the urgent safety measure (Protocol Amendment 4), patients will no longer receive the 3q4wk schedule; instead tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg will be administered once q3wk, on Day 1 of each 21-day cycle.

6 out of 24 patients were originally treated at 1.2 mg/kg 3q4wk then changed to 2.0 mg/kg once q3wk and 4 patients started on 2.0 mg/kg once q3wk. The first 14 patients followed the 1.2 mg/kg 3q4wk treatment regime throughout.

3.1 Sample Size Considerations

In the Cohort Expansion part, up to 20-30 patients in two indication arms (cervical and ovarian) are expected to provide more information on the safety of the compound at the RP2D level as well as preliminary efficacy data for the more frequent dosing regimen.

3.2 Randomization

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

3.3 Schedule of Assessments

A trial flowchart is shown in Appendix 6.

4.0 Study Variables and Covariates

4.1 Primary Variable

The primary endpoint is the evaluation of Adverse Events (AEs):

- Incidence of AEs,
- Incidence of serious AEs (SAEs),
- Incidence of infusion-related AEs,
- Incidence of Adverse Events with Common Toxicity Criteria for Adverse Events (CTCAE) grade ≥ 3 AEs
- Incidence of AEs related to trial drug during the trial.

4.2 Secondary Variables

The secondary endpoints are as follows:-

- Safety laboratory parameters
  - Hematology
  - Biochemistry
  - Coagulation factors
  - Flow cytometry
- Skin disorders
- Bleeding events
- Neuropathy
- PK parameters of tisotumab vedotin (Humax-TF-ADC) , non-conjugated HuMax-TF and free toxin [monomethyl auristatin E, (MMAE)]
  - clearance
  - volume of distribution
  - area-under-the-concentration-time curve [AUC0 last and AUC0-∞]
  - maximum concentration [Cmax] and time of Cmax [Tmax]
  - pre-dose values before each dose (Ctrough)
  - half-life
- Immunogenicity of tisotumab vedotin (human anti-human antibodies)
- Anti-tumor activity measured by:
  - tumor shrinkage (based on computerized tomography [CT] scan evaluations)
  - change in Cancer Antigen 125 (CA 125)
- Efficacy endpoints:
  - Objective Response (Complete Response [CR] or Partial Response [PR]),
  - Disease Control (CR, PR or SD),

- Progression-Free Survival (PFS)
- Duration of Response (DoR)

4.3 Research Variables

Research endpoints:

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

4.4 Predetermined Covariates and Prognostic Factors

NA

5.0 Definitions

5.1 Baseline

Baseline is defined as the latest available measurement made before the first treatment with tisotumab vedotin (HuMax-TF-ADC).

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 in accordance with the RECIST criteria version 1.1 (Eisenhauer et al, 2009), where appropriate. However, specific guidelines may be used (i.e., Rustin et al., 2004 for ovarian cancer).

Response will be categorized as CR, PR, SD or Progressive Disease (PD).

Response will be assessed from the results of CT-scans at the Screening Visit and at the end of every cycle (i.e., on Day 1 of Cycles 2 to 9). Additional scan at the End of Trial Visit (EOT) Visits are to be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.

CA 125 is assessed, and analyzed at a central laboratory, for patients with ovarian cancer. 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 2 weeks prior to starting treatment.

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 4 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 6 weeks (± 7 days) after first treatment.

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 CR or PR at the time point (with a window of ±7 days), or have an evaluation of SD, PR or CR at any point from the time point minus 7 days or later.

Response Evaluation and Reporting of Results

The response evaluation recorded in the eCRF will be used in analysis.

Each patient will be assigned one of the following categories:

1) CR

2) PR

3) SD

4) PD or

5) Not Evaluable

Patients in response categories 1 and 2 are considered responders and patients in response categories 4 and 5 are considered as failing to respond to treatment (disease progression). Patients in response categories 1, 2 and 3 are considered to be in disease control.

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. This will be assessed at the end of study.

Best overall response will be categorized into responders and non-responders as defined in Section 5.2.

If a patient withdraws with no post-baseline assessment of response, then they will be categorized as 'Not Evaluable' and classed as being a non-responder.

Confirmation

SD: follow-up measurements must have met the SD criteria at least once and for a minimum time period of 6 weeks (± 7 days) after first treatment.

5.4 Progression Free Survival

Progression-free survival (PFS) is defined as the number of weeks from Day 1 in Cycle 1 to first PD or death. Progression-free survival will be derived for all patients and presented graphically as well as summarized using survival analysis methods.

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.

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

5.5 Duration of Response

Duration of response is defined as the number of weeks from the first documentation of objective tumor response (CR or PR) to the date of first PD or death. 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.

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 $(m)^2$)

6.0 Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) will comprise all patients who have been exposed to the trial drug. This population will be used for evaluation of all endpoints, with the exception of PK.

6.2 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PK) will comprise all patients who have been exposed to the trial drug and have at least one PK assessment after the first dose of study medication. This population will be used for evaluation of all PK endpoints.

7.0 Interim Analyses

No interim analysis is planned.

A Data Monitoring Committee (DMC) reviewed the data from each dose cohort in the dose escalation part of the study to determine whether the dose would be escalated. An explanation of this process and the dose escalation rules are given in the protocol and further details are provided in the DMC charter.
The DMC can propose and the sponsor's Safety committee endorse whether the trial should continue, be modified, the dose be reduced, or whether the study should be discontinued permanently.
A DMC evaluated safety data during the Dose Escalation part of the trial and will not hold any pre-planned meetings but will convene in the event of safety signals in the Cohort Expansion part of the trial.
At the time of writing the SAP no tables, figures, and listings (TFL) are planned for the DMC.

8.0 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 Quality 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, 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.

9.0 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. All summaries presenting frequencies and incidences will include n, % and N, where N is the total number of patients with recorded values in the corresponding group. 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 2 additional decimal places, up to a maximum of 4 decimal places.

All confidence intervals will be 2-sided 95% confidence intervals.

No formal statistical tests will be performed.

A patient will be considered as having completed the trial when all planned trial visits have been performed.

No imputation of missing data is planned for safety endpoints and PK endpoints, except in the calculation of derived variables as described in Section 5.

If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

Individual patient listings including information on actual dose will also be presented.

Summary statistics will be presented as follows:

- For treatment Cycle 1: by cancer type and total
- For all treatment cycles: by cancer type and total

All data will be listed. Listings will be sorted by cancer type, patient number and time of assessment (where applicable).

All TFLs, except for PK, will be presented for subject's dose regimens as follows:

- All
- *3Q4W*
- *3Q4WK switched to Q3WK*
- *Q3WK*

PK TFLs, will be presented for subject's dose regimens as follows:

- *3Q4W*
- *3Q4WK switched to Q3WK*
- *Q3WK*

9.1 Subgroups and Center Effects

Subgroup analyses for the following factors are planned:

- TF expression
- ADA positivity

Details of subgroup analysis are given under the related section. Other sub-group analyses may be performed post-hoc. Due to the low number of patients per center no investigation of center effects are planned.

9.2 Subject Disposition

The number and percentage of patients screened, enrolled, and in the FAS will be presented, together with the number and percentage of patients who completed 4 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.

9.3 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.

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

9.4 Treatments

9.4.1 Extent of Study Drug Exposure

The total duration of exposure in days as defined in Section 5.0 will be summarized.

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

9.4.2 Concomitant Medications

Medications received concomitantly with study drug will be categorized by medication coded term according to WHODRUG dictionary (WHODRUG2017Mar01DDEB2 or later), 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.

9.5 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 (Version 20.0 or later), and summarized by the number and percentage of patients with at least one medical history in each system organ class and preferred term category.

Additional medical history will be listed for:

- Peripheral Neuropathy
- Ophthalmology

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, and the 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.

Demography listings will be repeated and sorted by the following subgroups:-

- TF expression
- ADA positivity(positive/non-positive)

9.6 Safety Analysis

9.6.1 Adverse Events

AEs will be coded using MedDRA (Version 20.0 or later). The severity of the AEs will be recorded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (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 dose 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), 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, infusion-related AEs and ophthalmology (conjunctivitis and keratitis). These will be identified as described in Table 2 below, where PT=Preferred Term, and HLT=High Level Term.

Table 2: List of AEs of Special Interest

Skin Rash	PT: Drug eruption, Lip ulceration, Rash, Rash maculo-papular, Rash pustular
Bleeding	PT: Epistaxis, Haematochezia, Haematuria, Haemoptysis, Laryngeal haemorrhage, Melaena, Pulmonary haemorrhage, Rectal haemorrhage, Vaginal haemorrhage
Neuropathy	PT: Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy
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)	All AEs ticked by the investigator to be IRR's on the AE form

Ophthalmology	PT: Blepharitis
	PT: Conjunctivitis
	PT: Conjunctivitis bacterial
	PT: Conjunctivitis viral
	PT: Eye irritation
	PT: Eye pain
	PT:Keratitis
	PT: Meibomianitis
	PT: Punctate keratitis
	PT: Symblepharon
	PT: Visual Impairment
	PT: Vital dye staining cornea present

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 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, neuropathy and ophthalmology 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..

A further figure will be produced which is a bar graph of all adverse events by cycle and cancer type, 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, study treatment related AEs, AEs occurring in Cycle 1 and AEs of special interest will be produced.

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.

The overall summary of AEs, SAEs and AEs with CTCAE grade≥3, will be repeated for the following subgroups:-

- TF expression
- ADA positivity(positive/non-positive)

A bar chart will be produced showing major safety signals (CTCAE grade ≥ 3) by ADA results (positive/non-positive).

9.6.2 Laboratory Safety Data

Hematology, biochemistry and coagulation parameters will be analyzed at a central laboratory. Values will be presented in SI units. The following parameters are assessed:

Hematology: Red Blood Cell Count; Hemoglobin; Hematocrit; Mean Corpuscular Hemoglobin; Mean Corpuscular Hemoglobin Concentration; Mean Corpuscular Volume; White Blood Cell Count; Neutrophils, Absolute; Lymphocytes, Absolute; Monocytes, Absolute; Eosinophils, Absolute; Basophils, Absolute; 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, Ferritin, C-Reactive Protein, Glycosylated Hemoglobin.

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

Summaries of the actual values at baseline and percentage change from baseline at each post-baseline visit 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.

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 cancer type for each parameter.

Pregnancy test results will also be listed.

Glomerular filtration rate, recorded on the eCRF will also be listed.

9.6.2.1 Flow Cytometry

Samples for assessment of flow cytometry will be collected at Screening and 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+)
- B-cells (CD45+CD19+)

Summaries for flow cytometry will show the actual values at baseline and percentage change from baseline at each post-baseline visit will be presented at each visit, and individual results for each patient will be listed.

9.6.2.2 Hepatitis B, C, HPV and Cytomegalovirus Serology

Blood samples will be drawn for assessment of the following parameters, at Screening and End of Trialvisits, and will be analyzed in a central laboratory.

- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Surface Antibody (Anti-HBs, HBsAb)
- Hepatitits B Core Antibody (Anti-HBc, HBcAb)
- Hepatitis C Antibody (Anti-HCV)
- Cytomegalovirus IgG (CMV IgG)
- Cytomegalovirus IgM (CMV IgM)
- Human Papillomavirus (HPV-cervical screen)

If Hepatitis C or CMV IgM is Positive, a polymerase chain reaction (PCR) will be done to confirm results. 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.

9.6.2.3 Ophthalmology

Listings of Ophthalmology data will be provided for

- Visual Acuity
- Schimer's Tear Test
- SLIT Lamp
- Interocular Pressure
- Fundoscopy
- Overall Evaluation
- Treatment initiated/adjusted

9.6.2.4 Other Clinical Safety Data

9.6.2.4.1 Vital Signs

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

Vital Signs Assessments during the Cohort Expansion Part for Cycle 1 to 9 are made at the following times at visits where infusions are given:

- Pre-infusion (including weight)
- At the end of infusion (± 5 min)
- 2 hours after end of infusion (± 15 min)

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.

A 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.

9.6.2.4.2 Physical Examinations

Physical examination data will be collected at Screening, Day 1 of Cycle 1 and 2 and End of Study.

A 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.

9.6.2.4.3 ECGs

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 3 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.

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

9.6.2.4.4 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.

9.7 Pharmacokinetic Analyses

9.7.1 Pharmacokinetic Concentrations

Two assays will be used for tisotumab vedotin (HuMax-TF-ADC), one detecting tisotumab vedotin (HuMax-TF-ADC) only and one detecting tisotumab vedotin (HuMax-TF-ADC) and non-conjugated Humax-TF.

Blood samples for assessment of HuMax-TF-ADC, non-conjugated HuMax-TF and MMAE will be drawn for central analysis in accordance to the timing provided in Table 4 of Appendix 6.

[redacted]

Plasma concentrations will be summarized for tisotumab vedotin (Humax-TF-ADC), non-conjugated 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 $\sigma 2$ 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, non-conjugated HuMax-TF and MMAE. These plots will show time in days post dose, and in these plots the values below LLOQ values will be set to 1/2 LLOQ. Linear plots of mean trough level with standard

deviations will be presented to assess attainment of steady state for tisotumab vedotin (Humax-TF-ADC), non-conjugated HuMax-TF and MMAE.

All individual patient plasma concentration data will be listed.

9.7.2 Pharmacokinetic Parameters

PK parameters for tisotumab vedotin (Humax-TF-ADC), non-conjugated HuMax-TF and free toxin (MMAE) will be estimated using noncompartmental methods with Phoenix WinNonlin® 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 or at the end of a profile should be set to "missing". If there are more than 2 consecutive <LLOQ concentrations after C_{max} followed by samples >LLOQ, 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. Prior to analysis, data sets should be reviewed to ensure there is an actual time > 0.00 that corresponds to each concentration value measured (whether or not > LLOQ)

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.

Individual curves of plasma/serum concentration of tisotumab vedotin (Humax-TF-ADC), HuMax-TF and free toxin (MMAE), including information on actual dose, will be presented for all patients. All available data will be shown in these figures. The patient number and dosing regimen will be presented as a subtitle.

For cycle 1, 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	C_{max} 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.	T_{max} from WNL
AUCs	Calculated by the linear trapezoidal linear interpolation method, 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	AUC_{last} from WNL

Parameter	Description	SAS Programming Notes
	number of nonmissing samples at 0 to t hours.	
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity. Calculated as AUC_0-inf = AUC0-t+ Clast/λz, where Clast is the last measurable analyte concentration and λz is the terminal elimination rate constant, expressed in inverted units of time.	AUC_{INF_obs} from WNL If Rsq ≤ .80 or AUC_%Extrap_obs >20% then parameter is deleted
%AUCext	percentage of the AUC that is due to the extrapolation Calculated as %AUCext = ([AUCinf – AUClast]/AUCinf) * 100	AUC_%Extrap_obs
$t_{1/2}$	Half-life, expressed in time units. Calculated as ln(2)/λz, 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
λz	K_{el} or lambda z, Apparent first-order terminal-elimination rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least 3 points and an r^2 greater than 0.80 are required to retain λz and associated parameters (t1/2, AUC0-inf, CL and Vz)	Lambda_z from WNL If Rsq ≤ .80 then parameter is deleted
CL	Total clearance (IV), expressed in volume / time unit. Calculated as:	Cl_obs from WNL If Rsq ≤ .80 or AUC_%Extrap_obs

Parameter	Description	SAS Programming Notes
	CL = Dose (iv)/AUC0-inf	>20% then parameter is deleted
Vz	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 non-conjugated HuMax-TF, the dose will be assumed to be 97% of the total dose and the dose of MMAE will be assumed to be 0.82%

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 1-9.

All PK parameters will be calculated separately for Cycle 1 overall and for the three different dosing periods within Cycle 1. C_{trough} will consist of all pre-dose values on each Day 1 of cycles 1 to 9.

If deemed applicable compartmental modeling approaches to parameter estimation will be applied.

Scatter plots of Cmax versus cancer type will be presented by cycle.

Further exploratory analyses of PK data may be performed.

The following figures will be presented by ADA results (positive/non-positive)

- mean pre-dose and Cmax tisotumab vedotin (Humax-TF-ADC) plasma concentrations versus time
- mean pre-dose Non-conjugated HuMax-TF Plasma Concentrations versus time
- mean pre-dose MMAE Plasma Concentrations versus time
- Cmax by cancer type and ADA by cycle

9.8 Immunogenicity

Blood samples will be taken for analysis of ADA, both total and neutralizing, at Screening, Day 1 of each cycle, results will be obtained as positive or negative.

Titers of tisotumab vedotin (Humax-TF-ADC) will be listed and positive/negative host immune response to tisotumab vedotin (Humax-TF-ADC) will be summarized (positive/negative).Summary tables presenting number and percentage of patients with positive/negative results at each visit and a positive result any time post-baseline will be presented.

9.9 Efficacy Analyses

All individual scan data and CA 125 values, and all derived efficacy variables will be listed for each patient.

9.9.1 Response

Objective response (CR or PR) rate will be determined along with the corresponding two-sided 95% exact binomial confidence interval.

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.

Best Overall Response will be evaluated and summarized. Number and percentage of patients in each category and who are responders/non-responders and confirmed responders will be presented, together with a 95% confidence interval calculated using the Clopper-Pearson exact method.

These summaries will be presented by cancer type.

In addition, for patients with ovarian cancer, response according to CA-125 will be assessed, and this will be summarized as the number and percentage of patients with a response.

Summaries of Objective Response, Best Overall Response will be provided for the following subgroups:-

- TF expression (Membrane H-Score <50, Membrane H-Score >=50 and <100, Membrane H-Score >=100)
- ADA positivity(positive/non-positive)

9.9.2 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.

The quartile estimates of PFS and DoR from the Kaplan Meier product limit algorithm will be presented (Kaplan and Meier, 1958). The two-sided 95% confidence interval will be presented as well. The number of events may be small, and thereby limit use of the Kaplan Meier method to provide reliable information. In this case, descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum) for PFS or DoR will be presented.

Summaries of PFS will be provided for the following subgroups:-

- TF expression
- ADA positivity (positive/non-positive)

9.9.3 Duration of Response

Kaplan-Meier estimates and 95% confidence intervals for duration of response (DoR) 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 DoR 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.

Summaries of DoR will be provided for the following subgroups:-

- TF expression
- ADA positivity (positive/non-positive)

A separate summary of duration of response will be produced including subjects with non-confirmed response as well as confirmed response.

9.9.4 Tumor Shrinkage

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

An additional waterfall plot will be provided showing results by ADA result (positive/non-positive).

9.9.5 CA 125

Summary statistics of 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

9.10 Research Endpoints

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

Results will be listed and plots of individual patient data over time (actual values and percent change from baseline) will be produced for these parameters

10.0 Validation

[redacted]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.

11.0 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.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-47

Rustin GJ, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Nat Cancer Inst.* 2004;96:487-8

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

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
3q4wk	Three times every four weeks
ADC	Antibody-drug antibody
AE	Adverse event
ATC	Anatomic Therapeutic Classification
AUC	Area-under-the-concentration-time curve
CA 125	Cancer Antigen 125
cfDNA	Cell-free deoxyribonucleic acid
C_{max}	Maximum concentration
CR	Complete Response
CRPC	Castration-resistant prostate cancer
CT	Computerized tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DoR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HuMax-TF-ADC	HuMax® tissue factor antibody drug conjugate
MMAE	Monomethyl auristatin E
MTD	Maximum tolerated dose
NCI	National Cancer Institute
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PSA	Prostate specific antigen
RP2D	Recommended dose for phase II trials
q3wk	One time every three weeks
QoL	Quality of Life
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event

SD	Stable Disease
Std	Standard Deviation
TF	Tissue factor
TFL	Tables, figures and listings
T_{max}	Time of C_{max}
TNM	Tumor Nodes Metastases

Appendix 2 List of In-Text Tables, Figures, and Listings

NA

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:		
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Appendix 4 List of DMC Tables, Figures, Listings

n/a

Appendix 5 List of Additional Protocol Violation/ Protocol Deviation Identification Listings

NA

Appendix 6 Schedule of Assessments Cohort Expansion Part

Table 3: Trial Flow Chart – Cohort Expansion Part

Treatment Cycle	Screening	Cycle 1					Cycle 2-9				EOT [1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	**0**	**1[3]**	**2[3]**	**3[3]**	**4**	**5**	**1[3]**	**2[3]**	**3[3]**	**4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**18d**	**22d**	**1d**	**8d**	**15d**	**22d**	**-**	**30 days after last dosing**	**-**
Visit window[4]		**-**	**±1d**	**±1d**	**-±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**-**	**±14d**	**-**
Informed Consent	X[5]												
Eligibility Criteria	X												
Demographics	X												
Medical History[6]	X												
Height and Body Weight[7]	X	X					X				X		
Physical Examination	X	X									X		
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X		X[9]
ECG[10]	X	X					X				X		X[9]
CT-Scan	X[11]						X[12]				X[12]		X[9]
ECOG Performance Status	X	X					X				X		X[9]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X[9]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X		X[9]
Trial Drug Administration[22]		X	X	X			X	X	X				
Bleeding Assessment	X	X				X	X				X		X
Skin Assessment	X	X				X	X				X		X
Neuropathy Assessment	X	X				X	X				X		X
Ophthalmological Evaluation	X					X[13]				X[13]	X[13]		X[13]
Radionuclide Bone Scan[14]	X						X						X[9]
LABORATORY ASSESSMENTS[15]													
Hematology	X	X	X	X	X	X	X	X	X	X	X		X[9]
Biochemistry	X	X	X	X	X	X	X	X	X	X	X		X[9]

Treatment Cycle	Screening	Cycle 1					Cycle 2-9				EOT [1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	**0**	**1[3]**	**2[3]**	**3[3]**	**4**	**5**	**1[3]**	**2[3]**	**3[3]**	**4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**18d**	**22d**	**1d**	**8d**	**15d**	**22d**	**-**	**30 days after last dosing**	**-**
Visit window[4]		**-**	**±1d**	**±1d**	**-±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**-**	**±14d**	**-**
Coagulation factors	X	X	X	X	X	X	X	X	X	X	X		X[9]
PSA[14]	X	X					X				X		X[10]
CA 125[16]	X	X					X				X		X[10]
Flow Cytometry		X[17]					X[17]				X		X[10]
Pregnancy Test	X	X					X				X		X[10]
ADA (Immunogenicity)	X	X					X						X[10]
Hepatitis B, C, CMV, HPV[18]	X										X		X[10]
PK Sampling[19]	X	X	X	X	X	X	X	X	X				X[10]
Tumor biopsy	X[20]												X[10]
Biomarker	X								X[21]				

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CRPC=Castration-resistant prostate cancer; CT=computerized tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Trial; HBc=Hepatitis B core; HBs=Hepatitis B surface; HBsAg=Hepatitis B surface antigen; HCV=hepatitis C virus; HPV= human papilloma virus; Ig=Immunoglobulin; PCR=polymerase chain reaction; PD=progressive disease; PK=pharmacokinetic; PSA=prostate specific antigen; SAE=serious adverse event

Footnotes to Trial Flowchart: Cohort Expansion Part
[1] If the patient shows PD, is to start new anti-cancer treatment or withdraws from trial due to another reason during treatment, the EOT Visit should be performed as soon as possible after decision of withdrawal.
[2] Only SAEs will be assessed.
[3] The patient shall stay at hospital for at least 2 hours after the infusion and may be requested to stay longer at the discretion of the investigator.
[4] The specified visit windows are in accordance with the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ± 3 days after Day 22 of the previous cycle.
[5] Informed consent must be obtained before or at the Screening Visit window i.e., may be reasonably prior to the screening date.
[6] Signs and symptoms occurring between Visit 0 and first infusion should be recorded as medical history (see Protocol Section 10 for details). SAEs should be reported as of the signing of the informed consent.

Footnotes to Trial Flowchart: Cohort Expansion Part
[7] Height is only assessed at the Screening Visit. During the trial, only body weight is measured on the first dosing day in a cycle, as part of the dose calculation. If body weight is assessed ≤ 7days before the first day of the planned dosing in a cycle, this value can be used to calculate dose.
[8] Temperature, blood pressure and heart rate. Within each visit, preferably the same equipment shall be used for vital signs measurements. Vital signs should be assessed just before and no longer than 30 minutes before *infusion start*, during and after the infusions until 2 hours after end of infusions, as indicated in Protocol Section 10.5
[9] Optional.
[10] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before infusion of the trial drug on Visit 1 for all cycles, in accordance with the ECG Specifications Manual.
[11] Within 4 weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed as part of the screening procedure. If a CT-scan has been performed within 4 weeks prior to Visit C1-V1 as part of standard procedure, it is acceptable as screening CT-scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.
[12] At the end of every second cycle, i.e., on Day 1 of Cycles 3, 5, 7 and 9, CT-scans can be performed up to 7 days before Day 1 of the relevant cycle to ensure result to be available before subsequent dosing. Additional scan at the EOT Visit. To be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.
[13] Patients experiencing ocular symptoms must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).
[14] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every 16 weeks (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed 12 weeks later. The screening radionuclide bone scan can be performed up to 4 weeks prior to Visit C1-V1.
[15] Laboratory parameters will be analyzed centrally.
[16] For patients with ovarian and endometrial cancer.
[17] Flow cytometry only on Cycle 1 and Cycle 5.
[18] HBsAg, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients; for CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV PCR; for HCV, anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR. HPV only for patients with cervical cancer. At EOT, only antibodies to CMV antigen will be assessed.
[19] See Protocol Table 4 and Section 10.17 for details of PK samplings.
[20] Archived biopsy material can be forwarded if a sample is available. If no sample is available, a new tumor biopsy must be obtained at least 2 weeks before dosing to ensure healing of wound.
[21] Only on Cycle 4.
[22] Preventive eye therapy to be administered in relation to infusions as detailed in Protocol Section 8.4.5.3.

Table 4: PK Sampling - Cohort Expansion Part

Treatment Cycle	Screening	Cycle 1					Cycle 2-9			Unscheduled
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**1-X**
Day/Week	**-**	**1d**	**8d**	**15d**	**18d**	**22d**	**1d**	**8d**	**15d**	
Before Infusion (on infusion days)	X	X	X	X	X	X	X	X	X	X[2]
End of infusion (+15 minutes) [1]		X					X			
+ 2 hours (± 15 minutes) after end of infusion [1]		X								

[1] Allowed time windows are indicated in parentheses.
[2] Optional.

Appendix 7 Schedule of Assessments Cohort Expansion Part- After Urgent Safety Measure

Table 5: Trial Flow Chart – Cohort Expansion Part - After Urgent Safety Measure

Treatment Cycle	Screening	Cycle 1			Cycle 2-9			EOT[1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	**0**	**1[3]**	**2**	**3**	**1[3]**	**2**	**3**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30 days after last dosing**	**-**
Visit window[4]		**-**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**-**	**±14d**	**-**
Informed Consent	X[5]									
Eligibility Criteria	X									
Demographics	X									
Medical History[6]	X									
Height and Body Weight[7]	X	X			X			X		
Physical Examination	X	X						X		
Vital Signs[8]	X	X	X	X	X		X	X		X[9]
ECG[10]	X	X			X			X		X[9]
CT-Scan	X[11]				X[12]			X[12]		X[9]
ECOG Performance Status	X	X			X			X		X[9]
Adverse Events	X	X	X	X	X		X	X	X	X[9]
Concomitant Medication	X	X	X	X	X		X	X		X[9]
Trial Drug Administration[22]		X			X					
Bleeding Assessment	X	X		X	X			X		X
Skin Assessment	X	X		X	X			X		X
Neuropathy Assessment	X	X		X	X			X		X
Ophthalmological Evaluation	X			X[13]			X[13]	X[13]		X[13]
Radionuclide Bone Scan[14]	X				X					X[9]
LABORATORY ASSESSMENTS[15]										
Hematology	X	X	X	X	X	X	X	X		X[9]
Biochemistry	X	X	X	X	X	X	X	X		X[9]
Coagulation factors	X	X	X	X	X	X	X	X		X[9]

Treatment Cycle	Screening	Cycle 1			Cycle 2-9			EOT[1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	**0**	**1[3]**	**2**	**3**	**1[3]**	**2**	**3**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30 days after last dosing**	**-**
Visit window[4]		**-**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**-**	**±14d**	**-**
PSA[14]	X	X			X			X		X[10]
CA 125[16]	X	X			X			X		X[10]
Flow Cytometry		X[17]			X[17]			X		X[10]
Pregnancy Test	X	X			X			X		X[10]
ADA (Immunogenicity)	X	X			X					X[10]
Hepatitis B, C, CMV, HPV[18]	X							X		X[10]
PK Sampling[19]	X	X	X	X	X	X	X			X[10]
Tumor biopsy	X[20]									X[10]
Biomarker	X						X[21]			

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CRPC=Castration-resistant prostate cancer; CT=computerized tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Trial; HBc=Hepatitis B core; HBs=Hepatitis B surface; HBsAg=Hepatitis B surface antigen; HCV=hepatitis C virus; HPV= human papilloma virus; Ig=Immunoglobulin; PCR=polymerase chain reaction; PD=progressive disease; PK=pharmacokinetic; PSA=prostate specific antigen; SAE=serious adverse event

Footnotes to Trial Flowchart: Cohort Expansion Part- After Urgent Safety Measure
[1] If the patient shows PD, is to start new anti-cancer treatment or withdraws from trial due to another reason during treatment, the EOT Visit should be performed as soon as possible after decision of withdrawal.
[2] Only SAEs will be assessed.
[3] The patient shall stay at hospital for at least 2 hours after the infusion and may be requested to stay longer at the discretion of the investigator.
[4] The specified visit windows are in accordance with the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ± 3 days after Day 15 of the previous cycle.
[5] Informed consent must be obtained before or at the Screening Visit window i.e., may be reasonably prior to the screening date.
[6] Signs and symptoms occurring between Visit 0 and first infusion should be recorded as medical history (see Protocol Section 10 for details). SAEs should be reported as of the signing of the informed consent.
[7] Height is only assessed at the Screening Visit. During the trial, only body weight is measured on the first dosing day in a cycle, as part of the dose calculation. If body weight is assessed ≤ 7days before the first day of the planned dosing in a cycle, this value can be used to calculate dose.

Footnotes to Trial Flowchart: Cohort Expansion Part- After Urgent Safety Measure
[8] Temperature, blood pressure and heart rate. Within each visit, preferably the same equipment shall be used for vital signs measurements. Vital signs should be assessed just before and no longer than 30 minutes before infusion start, during and after the infusions until 2 hours after end of infusions, as indicated in Protocol Section 10.5.
[9] Optional.
[10] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before infusion of the trial drug on Visit 1 for all cycles, in accordance with the ECG Specifications Manual.
[11] Within 4 weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed as part of the screening procedure. If a CT-scan has been performed within 4 weeks prior to Visit C1-V1 as part of standard procedure, it is acceptable as screening CT-scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.
[12] At the end of every second cycle, i.e., on Day 1 of Cycles 3, 5, 7 and 9, CT-scans can be performed up to 7 days before Day 1 of the relevant cycle to ensure result to be available before subsequent dosing. Additional scan at the EOT Visit. To be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.
[13] Patients experiencing ocular symptoms must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).
[14] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every 16 weeks (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed 12 weeks later. The screening radionuclide bone scan can be performed up to 4 weeks prior to Visit C1-V1.
[15] Laboratory parameters will be analyzed centrally.
[16] For patients with ovarian and endometrial cancer.
[17] Flow cytometry only on Cycle 1 and Cycle 5.
[18] HBsAg, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients; for CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV PCR; for HCV, anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR. HPV only for patients with cervical cancer. At EOT, only antibodies to CMV antigen will be assessed.
[19] See Protocol Table 4and Protocol Section 10.17 for details of PK samplings.
[20] Archived biopsy material can be forwarded if a sample is available. If no sample is available, a new tumor biopsy must be obtained at least 2 weeks before dosing to ensure healing of wound.
[21] Only on Cycle 4.
[22] Preventive eye therapy to be administered in relation to infusions as detailed in Protocol Section 8.4.5.3

Table 6: PK Sampling - Cohort Expansion Part - After Urgent Safety Measure

Treatment Cycle	Screening	Cycle 1			Cycle 2-9			Unscheduled
Visit Number	**0**	**1**	**2**	**3**	**1**	**2**	**3**	**1-X**
Day/Week	**-**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	
Before Infusion (on infusion days)	X	X	X	X	X	X	X	X[2]
End of infusion (+15 minutes) [1]		X			X			
+ 2 hours (± 15 minutes) after end of infusion [1]		X						

[1] Allowed time windows are indicated in parentheses.
[2] Optional.

Statistical Analysis Plan

Sponsor:	Genmab A/S
Protocol No:	GEN702
Version No./Date	Final 5.0 (incorporating Protocol Amendment 4), 06 Jul 2017
Title	DOSE-ESCALATING AND COHORT EXPANSION SAFETY TRIAL 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	6.0, 13 Sep 2016
[redacted]**Project Id:**	GNMG702X-GN702X
SAP Version No./Date:	1.1, 24 Apr 2018

Approvals

Sponsor

Sponsor Name: Genmab A/S

Representative/ Title: [redacted]

Signature /Date: [redacted]

Project Manager/Title: [redacted]

Signature /Date: [redacted]

Biostatistician / Title: [redacted]

Signature /Date: [redacted]

Table of Contents

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Genmab Protocol GEN702.

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 dated 06JUL2017 and eCRF dated 03SEP2016. 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

The protocol states the following:

Response evaluation will be performed by external medical experts in relevant cancer types in collaboration with the sponsor Medical Expert and a Statistician.

No independent response evaluation will be performed in this trial. Summary statistics will not be presented by cancer type although stated in the protocol

2.0 Study Objectives

2.1 Primary Study Objective

To establish the tolerability of HuMax® tissue factor antibody drug conjugate (HuMax-TF-ADC) dosed 3 times every 4 weeks (q4wk) in a mixed population of patients with specified solid tumors.

2.2 Secondary Study Objective

- To determine the maximum tolerated dose (MTD) and the recommended dose for phase II trials (RP2D) with HuMax TF-ADC dosed 3 times q4wk.
- To establish the pharmacokinetic (PK) profile of HuMax-TF-ADC dosed 3 times q4wk.
- To evaluate the anti-tumor activity of HuMax-TF-ADC dosed 3 times q4wk in a mixed population of patients with specified solid tumors.

3.0 Study Design

This is a phase I/II open-label, dose escalating and cohort expansion, safety trial of tisotumab vedotin (HuMax TF-ADC) dosed 3q4wk (Days 1, 8 and 15 of each 28-day cycle) in a mixed patient population with solid tumors to establish the safety profile.

The trial consists of two parts: A Dose Escalation part followed by a Cohort Expansion part. The Dose Escalation part is a phase I trial and the Cohort Expansion part is a phase II trial.

This SAP covers the dose escalation part only.

The dose escalation part of the trial will have a standard 3 (+3) design which will evaluate HuMax-TF-ADC at doses of 0.9 mg/kg and up to a maximum of 1.5 mg/kg (0.9, 1.2, and 1.5 mg/kg). In each dose cohort, the initial 3 patients must include at least 2 different cancer types. A planned 3 dose levels (plus a potential intermediate cohort) is anticipated to a maximum of 24 patients.

A Data Monitoring Committee (DMC) will evaluate safety data during the trial.

The criteria for defining dose limiting toxicities (DLTs) are provided in Table 3 of the protocol. In the absence of first cycle DLTs, doses are escalated in the subsequent cohorts, as deemed appropriate by

the DMC and confirmed by sponsor. If first cycle DLTs are observed, cohorts will be expanded from 3 to 6 patients. Depending on the nature of the observed event, the DMC may require that at least 1 patient of the additional 3 patients to be enrolled at the same dose level should have the same cancer type as the patient experiencing the event. If a patient withdraws prior to completing the first treatment cycle, the sponsor should replace the patient, unless the withdrawal is due to a DLT.

Depending on the nature of the DLT and the patient status, the DMC and the Safety Committee may allow a patient with a DLT to continue on the trial, potentially on a reduced dose.

The maximum possible tested dose will be 1.5 mg/kg. If ≥ 2 out of 6 patients experience a DLT at 0.9 mg/kg, dose reduction to a lower dose can be investigated.

In order to capture long-term safety signals at different dose cohorts, no intra-patient dose-escalation will be allowed. In each dose cohort, a minimum of 1 day between the administrations of the doses to the patients will be implemented.

The main trial period will encompass 4 treatment cycles and allow patients with potential benefit (defined as stable disease (SD) or better) to continue for up to 8 additional treatment cycles (for a maximum of 12 cycles in total).

If a specific safety signal is observed in any of the tested indications, the sponsor will retain the possibility to enroll more patients at the same dose level. The sponsor in collaboration with the DMC has the possibility to add intermediate dose cohorts to better define MTD.

3.1 Sample Size Considerations

A maximum of 24 patients are planned to be enrolled in the dose escalation part of the trial. As the primary objective of the trial is to establish the tolerability of HuMax-TF-ADC, the sample size is based only on the 3 (+3) dose escalation MTD design and the expected maximum of 3 dose levels (plus a potential intermediate dose cohort). The classical 3 (+3) dose escalation MTD design aims to determine MTD with the fewest possible patients exposed. Taking into account an anticipated screen failure rate of 30%, 18 to 35 patients will be screened.

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.

3.3 Schedule of Assessments

A trial flowchart is shown in Appendix 6.

4.0 Study Variables and Covariates

4.1 Primary Variable

The primary endpoint is the evaluation of Adverse Events (AEs):

- Incidence of AEs,
- Incidence of serious AEs(SAEs),
- Incidence of infusion-related AEs,
- Incidence of Common Toxicity Criteria for Adverse Events (CTCAE) grade ≥ 3 AEs
- Incidence of AEs related to trial drug during the trial.

4.2 Secondary Variables

The secondary endpoints are as follows:-

- Safety laboratory parameters
  - Hematology
  - Biochemistry
  - Coagulation factors
  - Flow cytometry
- Skin disorders
- Bleeding events
- Neuropathy
- PK parameters of Humax-TF-ADC, Humax-TF and free toxin [monomethyl auristatin E, MMAE]
  - clearance
  - volume of distribution
  - area-under-the-concentration-time curve [AUC0 last and AUC0-∞]
  - maximum concentration [Cmax] and time of Cmax [Tmax]
  - pre-dose values before each dose (Ctrough)
  - half-life
- Immunogenicity of HuMax-TF-ADC (human anti human antibodies)
- Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT] scan evaluations), change in prostate specific antigen (PSA) and Cancer Antigen 125 (CA 125)
- Objective Response (Complete Response [CR] or Partial Response [PR]), Disease Control (CR, PR or SD), Progression-Free Survival (PFS) and Duration of Response (DoR)

4.3 Research Variables

Research endpoints:

- TF expression in tumor biopsies
- Circulating TF

- Circulating cell-free deoxyribonucleic acid (cfDNA)

4.4 Predetermined Covariates and Prognostic Factors

NA

5.0 Definitions

5.1 Baseline

Baseline is defined as the latest available measurement made before the first treatment with HuMax-TF-ADC.

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 in accordance with the RECIST criteria version 1.1 (Eisenhauer et al, 2009), where appropriate. However, specific guidelines may be used (i.e., Rustin et al., 2004 for ovarian cancer and Scher et al., 2008 for prostate cancer).

Response will be categorized as CR, PR, SD or Progressive Disease (PD).

Response will be assessed from the results of CT-scans at the Screening Visit and at the end of every second cycle (i.e., on Day 1 of Cycles 3, 5, 7, 9 and 11). Additional scans on 21 days (± 7 days) after Day 15 of Cycle 12, and at the EOT Visit are to be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.

Radionuclide bone scan and PSA will be performed for Castration-resistant prostate cancer (CRPC) patients. Radionuclide bone scan will be performed at screening, every 16 weeks (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed 12 weeks later. For patients with CRPC, when the bone scan is the sole indicator of progression, PD is defined in bone when at least ≥ 2 new lesions are seen on the bone scan compared with a prior scan for trial entry. There are no validated criteria for response on radionuclide bone scan. For control/relief/eliminate endpoints, it is recommended that post-treatment changes are recorded as either "no new lesions" or "new lesions." However, PD at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later, in the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms. In case where visible lesions disappear, this should be confirmed at the next scheduled assessment too.

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.

Additionally, CA 125 is assessed for patients with ovarian cancer and for patients with endometrial cancer. 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 2 weeks prior to starting treatment.

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 4 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 6 weeks (± 7 days) after first treatment.

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 CR or PR at the time point (with a window of ±7 days), or have an evaluation of SD at any point from the time point minus 7 days or later.

Response Evaluation and Reporting of Results

The response evaluation recorded in the eCRF will be used in analysis.

Each patient will be assigned one of the following categories:

1) CR

2) PR

3) SD

4) PD or

5) Not Evaluable

Patients in response categories 1 and 2 are considered responders and patients in response categories 4 and 5 are considered as failing to respond to treatment (disease progression). Patients in response categories 1, 2 and 3 are considered to be in disease control.

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. This will be assessed at the end of study.

Best overall response will be categorized into responders and non-responders as defined in Section 5.2.

If a patient withdraws with no post-baseline assessment of response, then they will be categorized as 'Not Evaluable' and classed as being a non-responder.

Confirmation

SD: follow-up measurements must have met the SD criteria at least once and for a minimum time period of 6 weeks (± 7 days) after first treatment.

PR and CR: no formal confirmation response is required. However, a repeat CT-scan will be performed no less than 4 weeks (± 7 days) after the criteria for response is met to substantiate/confirm CT response (Protocol Section 10.7).

5.4 Progression Free Survival

Progression-free survival (PFS) is defined as the number of weeks from Day 1 in Cycle 1 to first PD or death. Progression-free survival will be derived for all patients and presented graphically as well as summarized using survival analysis methods.

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 60 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 60 days of the last visit on the study will be considered when determining whether a patient died for the purposes of analysis of PFS.

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 60 days after the previous visit with adequate assessments	Date of previous visit with adequate assessments	Censored

5.5 Duration of Response

Duration of response is defined as the number of weeks from the first documentation of objective tumor response (CR or PR) to the date of first PD or death. 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.

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 $(m)^2$)

6.0 Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) will comprise all patients who have been exposed to the trial drug. This population will be used for evaluation of all endpoints, with the exception of PK .

6.2 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PK) will comprise all patients who have been exposed to the trial drug and have at least one PK assessment after the first dose of study medication. This population will be used for evaluation of all PK endpoints.

7.0 Interim Analyses

No interim analysis is planned.

A Data Monitoring Committee (DMC) will review the data from each cohort to determine whether the dose will be escalated. 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 can propose and the sponsor's Safety committee endorse whether the protocol should continue, be modified, the dose be reduced, or whether the study should be discontinued permanently.

The tables, figures, and listings (TFL) planned for the DMC are listed in Appendix 4.

8.0 Data Review

8.1 Data Handling and Transfer

[redacted]ill 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 Quality 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]rogramming of analysis datasets, 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.

9.0 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. All summaries presenting frequencies and incidences will include n, % and N, where N is the total number of

patients with recorded values in the corresponding group. 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 2 additional decimal places, up to a maximum of 4 decimal places.

All confidence intervals will be 2-sided 95% confidence intervals.

No formal statistical tests will be performed.

A patient will be considered as having completed the trial when all planned trial visits have been performed.

No imputation of missing data is planned for safety endpoints and PK endpoints, except in the calculation of derived variables as described in Section 5.

If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

Individual patient profiles including information on actual dose will also be presented.

Summary statistics will be presented as follows:

- For treatment Cycle 1: by dose cohort and total
- For all treatment cycles: by dose cohort and total

All data will be listed. Listings will be sorted by dose cohort, patient number and time of assessment (where applicable).

9.1 Subgroups and Center Effects

Subgroup analyses for the following factors are planned:

- TF expression
- ADA positivity

Details of subgroup analysis are given under the related section. Other sub-group analyses may be performed post-hoc. Due to the low number of patients per center no investigation of center effects are planned.

9.2 Subject Disposition

The number and percentage of patients screened, enrolled, and in the FAS will be presented, together with the number and percentage of patients who completed 4 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.

9.3 Protocol Deviations and Violations

Protocol deviations and violations (PDV) will be entered into the PPD 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.

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

9.4 Treatments

9.4.1 Extent of Study Drug Exposure

The total duration of exposure in days as defined in Section 5.0 will be summarized.

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

9.4.2 Concomitant Medications

Medications received concomitantly with study drug will be categorized by medication coded term according to WHODRUG dictionary (WHODRUG2017Mar01DDEB2 or later), 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.

9.5 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 (Version 20.0 or later), 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.

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.

Demography listings will be repeated and sorted by the following subgroups:-

- TF expression
- ADA positivity(positive/non-positive)

9.6 Safety Analysis

9.6.1 Adverse Events

AEs will be coded using MedDRA (Version 20.0 or later). The severity of the AEs will be recorded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (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 dose 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), 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.

Table 2: List of AEs of Special Interest

Skin Rash	Any AE linked to a lesion on the skin assessment page of the eCRF
Bleeding	Any AE linked to a record on the bleeding page of the eCRF
Neuropathy	Any AE linked to a record on the neuropathy page of the eCRF
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)	All AEs ticked by the investigator to be IRR's on the AE form

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 system organ class 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 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 bleeding events, this will be done for major bleeding events in addition to all bleeding 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. For the bleeding events, separate plots will be produced for minor bleedings, major bleedings and all bleedings.

A further figure will be produced which is a bar graph of all adverse events by cycle and dose cohort, 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, study treatment related AEs, AEs occurring in Cycle 1 and AEs of special interest will be produced.

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.

The overall summary of AEs, SAEs and AEs with CTCAE grade≥3, will be repeated for the following subgroups:-

- TF expression
- ADA positivity(positive/non-positive)

A bar chart will be produced showing major safety signals (CTCAE grade ≥ 3) by ADA results (positive/non-positive).

9.6.2 Laboratory Safety Data

Hematology, biochemistry and coagulation factors will be analyzed at the site laboratory and results recorded on the eCRF. 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; Lymphocytes, Absolute; Monocytes, Absolute; Eosinophils, Absolute; Basophils, Absolute; Reticulocytes; Platelet Count

Biochemistry: Sodium, Potassium, Calcium, Magnesium, Creatinine, Urea, 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 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 cohort 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.

9.6.2.1 Flow Cytometry

Samples for assessment of flow cytometry will be collected at Screening and 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+).

Summaries for flow cytometry will show the actual values at baseline and percentage change from baseline at each post-baseline visit will be presented at each visit, and individual results for each patient will be listed.

9.6.2.2 Hepatitis B, C, HPV and Cytomegalovirus Serology

Blood samples will be drawn for assessment of the following parameters, at Screening and End of Study visits, and will be analyzed at the site.

- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Surface Antibody (Anti-HBs, HBsAb)
- Hepatitits B Core Antibody (Anti-HBc, HBcAb)
- Hepatitis C Antibody (HCV)
- Cytomegalovirus IgG (CMV IgG)
- Cytomegalovirus IgM (CMV IgM)
- Human Papillomavirus (HPV-cervical screen)

If Hepatitis C or CMV IgM is Positive, a polymerase chain reaction (PCR) will be done to confirm results. 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.

9.6.3 Clinical Safety Data

9.6.3.1 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.

9.6.3.2 Bleeding Events

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. There will also be separate tables and bar charts for bleeding with onset during Cycle 1.

9.6.3.3 Neuropathy

An assessment of neuropathy will be done at every visit except day 2, 16 and 18 of cycle 1. 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.

9.6.3.4 Other Clinical Safety Data

9.6.3.4.1 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.

A 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.

9.6.3.4.2 Physical Examinations

Physical examination data will be collected at Screening, Day 1 of Cycle 1 and 2 and End of Study.

A 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.

9.6.3.4.3 ECGs

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 3 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.

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

9.6.3.4.4 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.

9.7 Pharmacokinetic Analyses

9.7.1 Pharmacokinetic Concentrations

Blood samples for assessment of HuMax-TF-ADC, non-conjugated HuMax-TF and MMAE will be drawn for central analysis in accordance to the timing provided in Table 3 of Appendix 6.

[redacted]

Plasma concentrations will be summarized for HuMax-TF-ADC, non-conjugated 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 $\sigma 2$ 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, non-conjugated HuMax-TF and MMAE. These plots will show time in days post dose, and in these plots the values below LLOQ values will be set to 1/2 LLOQ. Linear plots of mean trough level with standard deviations will be presented to assess attainment of steady state for HuMax-TF-ADC, non-conjugated HuMax-TF and MMAE.

All individual patient plasma concentration data will be listed.

9.7.2 Pharmacokinetic Parameters

PK parameters for HuMax-TF-ADC, non-conjugated HuMax-TF and free toxin (MMAE) will be estimated using noncompartmental methods with Phoenix WinNonlin® 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 or at the end of a profile should be set to "missing". If there are more than 2 consecutive <LLOQ concentrations after C_{max} followed by samples >LLOQ, 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. Prior to analysis, data sets should be reviewed to ensure there is an actual time > 0.00 that corresponds to each concentration value measured (whether or not > LLOQ)

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.

Individual curves of plasma/serum concentration of HuMax-TF-ADC, HuMax-TF and free toxin (MMAE), including information on actual dose, will be presented for all patients. All available data will be shown in these figures.

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 linear interpolation method, 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
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity. Calculated as AUC0-inf = AUC0-t+ Clast/λz, 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
%AUCext	percentage of the AUC that is due to the extrapolation Calculated as	AUC_%Extrap_obs

Parameter	Description	SAS Programming Notes
	%AUCext = ([AUCinf – AUClast]/AUCinf) * 100	
$t_{1/2}$	Half-life, expressed in time units. Calculated as ln(2)/λz, 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
λz	K_{el} or lambda z, Apparent first-order terminal-elimination rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least 3 points and an r^2 greater than 0.80 are required to retain λz and associated parameters (t1/2, AUC0-inf, CL and Vz)	Lambda_z from WNL If Rsq ≤ .80 then parameter is deleted
CL	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	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 non-conjugated HuMax-TF, the dose will be assumed to be 97% of the total dose and the dose of MMAE will be assumed to be 0.82%

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 2. C_{trough} will consist of all pre-dose values on each Day 1 of cycles 1 to 12.

If deemed applicable compartmental modeling approaches to parameter estimation will be applied.

Scatter plots of Cmax versus dose will be presented by cycle.

Further exploratory analyses of PK data may be performed.

The following figures will be presented by ADA results (positive/non-positive)

- mean pre-dose and Cmax HuMax-TF-ADC plasma concentrations versus time
- mean pre-dose Non-conjugated HuMax-TF Plasma Concentrations versus time
- mean pre-dose MMAE Plasma Concentrations versus time
- Cmax by dose and ADA by cycle

9.8 Immunogenicity

Blood samples will be taken for analysis of ADA, both total and neutralizing, at Screening, Day 1 of each cycle, and all Follow-Up visits, and results will be obtained as positive or negative.

Titers of HuMax-TF-ADC will be listed and positive/negative host immune response to HuMax-TF-ADC will be summarized (positive/negative).Summary tables presenting number and percentage of patients with positive/negative results at each visit and a positive result any time post-baseline will be presented.

9.9 Efficacy Analyses

All individual scan data, PSA and CACA 125125 values, and all derived efficacy variables will be listed for each patient.

9.9.1 Response

Objective response (CR or PR) rate will be determined along with the corresponding two-sided 95% exact binomial confidence interval.

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.

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.

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 addition, for patients with ovarian cancer and those with endometrial cancer, 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.

Summaries of Objective Response, Best Overall Response will be provided for the following subgroups:-

- TF expression
- ADA positivity(positive/non-positive)

9.9.2 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.

The quartile estimates of PFS and DoR from the Kaplan Meier product limit algorithm will be presented (Kaplan and Meier, 1958). The two-sided 95% confidence interval will be presented as well. The number of events may be small, and thereby limit use of the Kaplan Meier method to provide reliable information. In this case, descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum) for PFS or DoR will be presented.

Summaries of PFS will be provided for the following subgroups:-

- TF expression
- ADA positivity (positive/non-positive)

9.9.3 Duration of Response

Kaplan-Meier estimates and 95% confidence intervals for duration of response (DoR) 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 DoR 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.

Summaries of DoR will be provided for the following subgroups:-

- TF expression
- ADA positivity (positive/non-positive)

9.9.4 Tumor Shrinkage

The maximum change from baseline in the sum of the 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.

An additional waterfall plot will be provided showing results by ADA result (positive/non-positive).

9.9.5 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

9.10 Research Endpoints

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

Results will be listed and plots of individual patient data over time (actual values and percent change from baseline) will be produced for these parameters

10.0 Validation

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

11.0 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.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-47

Rustin GJ, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Nat Cancer Inst.* 2004;96:487-8

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

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADC	Antibody-drug antibody
AE	Adverse event
ATC	Anatomic Therapeutic Classification
AUC	Area-under-the-concentration-time curve
CA-125	Cancer Antigen 125
cfDNA	Cell-free deoxyribonucleic acid
C_{max}	Maximum concentration
CR	Complete Response
CRPC	Castration-resistant prostate cancer
CT	Computerized tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DoR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HuMax-TF-ADC	HuMax® tissue factor antibody drug conjugate
MMAE	Monomethyl auristatin E
MTD	Maximum tolerated dose
NCI	National Cancer Institute
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PSA	Prostate specific antigen
QoL	Quality of Life
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Stable Disease
SoC	Standard of Care
Std	Standard Deviation

TF	Tissue factor
TFL	Tables, figures and listings
T_{max}	Time of C_{max}
TNM	Tumor Nodes Metastases

Appendix 2 List of In-Text Tables, Figures, and Listings

NA

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		
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Table 14.1.1.2	Enrollment by Center and Dose Cohort	(All Enrolled Patients)
Table 14.1.1.3	Significant Protocol Deviations by Dose Cohort	(All Enrolled Patients)
Table 14.1.1.4	Patients Remaining on Treatment by Cycle and Dose Cohort	(All Enrolled Patients)
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Table 14.1.3.1	Medical History by Dose Cohort	(Full Analysis Set)
Table 14.1.3.2	History of Cancer by Dose Cohort	(Full Analysis Set)
Table 14.1.3.3	Disease Stage by Dose Cohort	(Full Analysis Set)
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Table 14.1.4.5	Concomitant Medications on or After Last Infusion by Dose Cohort	(Full Analysis Set)
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Table 14.2.1.3	Summary of MMAE Plasma Concentrations (ng/mL) by Dose Cohort	(PK Analysis Set)
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Table 14.2.3	Summary of Bone Scan Results by Dose Cohort	(Full Analysis Set)
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Table 14.2.7.1	Kaplan-Meier Summary of Duration of Response (Investigator Assessment)	(Full Analysis Set)
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Appendix 5 List of Additional Protocol Violation/ Protocol Deviation Identification Listings

NA

Appendix 6 Schedule of Assessments

Treatment Cycle	Screening	Cycle 1							Cycle 2-4				Cycle 5-12[1]				Follow-up	EOT[2]	Withdrawal Safety Follow-up[3]	Unscheduled
Visit Number	**0**	**1[4]**	**2**	**3[4]**	**4[4]**	**5**	**6**	**7**	**1[4]**	**2[4]**	**3[4]**	**4**	**1[4]**	**2[4]**	**3[4]**	**4**	**1-4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**2d**	**8d**	**15d**	**16d**	**18d**	**22d**	**1d**	**8d**	**15 d**	**22 d**	**1d**	**8d**	**15d**	**22d**	**6 weekly**	**-**	**30 days after last dosing**	**-**
Visit window[5]		**-**	**-**	**±1d**	**±1d**	**+1d**	**±1 d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±7d**	**-**	**±14d**	**-**
Informed Consent	X[6]																			
Eligibility Criteria	X																			
Demographics	X																			
Medical History[7]	X																			
Height and Body Weight[8]	X	X							X				X					X		
Physical Examination	X[9]	X																X		
Vital Signs[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X[11]
ECG[12]	X	X							X				X					X		X[11]
CT-Scan	X[13]								X[14]				X[14]				X	X[14]		X[11]
ECOG Performance Status	X	X							X				X					X		X[11]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[11]
Trial Drug Administration		X		X	X				X	X	X		X	X	X					
Bleeding Assessment	X	X	X	X	X	X	X	X	X	X	X		X	X	X			X		

Treatment Cycle	Screening	Cycle 1							Cycle 2-4				Cycle 5-12[1]				Follow-up	EOT[2]	Withdrawal Safety Follow-up[3]	Unscheduled
Visit Number	**0**	**1[4]**	**2**	**3[4]**	**4[4]**	**5**	**6**	**7**	**1[4]**	**2[4]**	**3[4]**	**4**	**1[4]**	**2[4]**	**3[4]**	**4**	**1-4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**2d**	**8d**	**15d**	**16d**	**18d**	**22d**	**1d**	**8d**	**15 d**	**22 d**	**1d**	**8d**	**15d**	**22d**	**6 weekly**	**-**	**30 days after last dosing**	**-**
Visit window[5]		**-**	**-**	**±1d**	**±1d**	**+1d**	**±1 d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±7d**	**-**	**±14d**	**-**
Skin Assessment	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X		X[11]
Neuropathy Assessment	X	X		X	X			X	X	X	X	X	X	X	X	X	X	X		X[11]
Radionuclide Bone Scan[15]	X												X							X[11]
LABORATORY ASSESSMENTS[16]																				
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[11]
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[11]
Coagulation factors	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[11]
PSA[15]	X	X							X				X				X	X		X[11]
CA 125[17]	X	X							X				X				X	X		X[11]
Flow Cytometry		X[18]											X[18]					X		X[11]
Pregnancy Test	X	X							X				X				X	X		X[11]
ADA (Immunogenicity)	X	X							X				X				X			X[11]
Hepatitis B, C, CMV, HPV[19]	X																	X		X[11]
PK Sampling[20]	X	X	X	X	X	X	X	X	X	X	X		X	X	X					X[11]
Tumor biopsy	X[21]																			X[11]
Biomarkers	X												X[22]							

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CRPC=Castration-resistant prostate cancer; CT=computerized tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Trial; HBc=Hepatitis B core; HBs=Hepatitis B surface; HBsAg=Hepatitis B surface antigen; HCV=hepatitis C virus; HPV= human papilloma virus; Ig=Immunoglobulin; PCR=polymerase chain reaction; PD=progressive disease; PK=pharmacokinetic; PSA=prostate specific antigen; SAE=serious adverse event

Footnotes to Trial Flowchart
[1] Additional treatment only if patient shows response of SD or better.
[2] If the patient shows PD, is to start new anti-cancer treatment or withdraws from trial due to another reason during treatment or Follow-up period, the EOT Visit should be performed as soon as possible after decision of withdrawal. If patient completes all Follow-up visits, the EOT Visit should be performed four weeks after end of Follow-up Visit 4 period.
[3] For patients who withdraw from the trial before Follow-Up Visit 1. Only SAEs will be assessed.
[4] The patient shall stay at hospital for at least 2 hours after the infusion and may be requested to stay longer at the discretion of the investigator.
[5] The specified visit windows are in accordance with the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ± 3 days after Day 22 of the previous cycle.
[6] Informed consent must be obtained before or at the Screening Visit window i.e., may be reasonably prior to the screening date.
[7] Signs and symptoms occurring between Visit 0 and first infusion should be recorded as medical history (see Protocol Section 10 for details). SAEs should be reported as of the signing of the informed consent.
[8] Height is only assessed at the Screening Visit. During the trial, only body weight is measured on the first dosing day in a cycle, as part of the dose calculation. If body weight is assessed ≤ 3 days before the first day of the planned dosing in a cycle, this value can be used to calculate dose.
[9] Including a baseline visual acuity assessment at screening.
[10] Temperature, blood pressure and heart rate. Within each visit, preferably the same equipment shall be used for vital signs measurements. Vital signs should be assessed just before and no longer than 30 minutes before infusion start, during and after the infusions until 2 hours after end of infusions, as indicated in Protocol Section 10.5
[11] Optional.
[12] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before infusion of the trial drug on Visit 1 for all cycles, in accordance with the ECG Specifications Manual.
[13] Within four weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed as part of the screening procedure. If a CT-scan has been performed within four weeks prior to Visit C1-V1 as part of standard procedure, it is acceptable as screening CT-scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.
[14] At the end of every second cycle, i.e., on Day 1 of Cycles 3, 5, 7, 9 and 11, CT-scans can be performed up to 7 days before Day 1 of the relevant cycle to ensure result to be available before subsequent dosing. Additional scans on 21 days (± 7 days) after Day 15 of Cycle 12, and at the EOT Visit. To be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.
[15] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every 16 weeks (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed twelve weeks later. The screening radionuclide bone scan can be performed up to four weeks prior to Visit C1-V1.
[16] Hematology, biochemistry, serology and pregnancy test will be analyzed locally at the sites. All other laboratory parameters will be analyzed centrally.
[17] For patients with ovarian and endometrial cancer.
[18] Flow cytometry only on Cycle 1 and Cycle 5.
[19] $HBsAg_n$, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients; for CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV PCR; for HCV, anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR. HPV only for patients with cervical cancer. At EOT, only antibodies to CMV antigen will be assessed.
[20] See Table 3 for details of PK samplings.

[21] Archived biopsy material can be forwarded if a sample is available. If no sample is available, a new tumor biopsy must be obtained at least 2 weeks before dosing to ensure healing of wound.
[22] Only on Cycle 5.

Table 3: PK Sampling

Treatment Cycle	Screening	Cycle 1							Cycle 2–4				Cycle 5–12				Unscheduled
Visit Number	0	1	2	3	4	5	6	7	1	2	3	4	1	2	3	4	1-X
Day/Week	-	1d	2d	8d	15d	16d	18d	22d	1d	8d	15d	22d	1d	8d	15d	22d	
Before Infusion *(on infusion days)*	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X[2]
End of infusion *(+15 minutes)* [1]		X		X	X				X	X	X		X	X	X		
+ 2 hours *(± 15 minutes)* after end of infusion [1]		X		X	X												

[1] Allowed time windows are indicated in parentheses.
[2] Optional.