PROTOCOL AND SUMMARY OF PROTOCOL AMENDMENTS

First-In-Human, Dose Escalating Safety Study of Tissue Factor Specific Antibody-Drug Conjugate Tisotumab Vedotin (Humax®-TF-ADC) in Patients with Locally Advanced and/or Metastatic Solid Tumors Known to Express Tissue Factor

Protocol no.:	GEN701
Trial name	innovaTV 201
ClinicalTrials.gov Identifier	NCT02001623
Sponsor:	Genmab A/S
Collaborators:	Seattle Genetics, Inc.
EudraCT No.:	2013-001074-15
IND No.:	115906
IMP Name:	Tisotumab vedotin (HuMax®-TF-ADC)
Development Phase:	1/2

*Genmab is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Genmab trials may vary, such as, but not limited to Genmab Holding B.V.; Genmab A/S; or Genmab US, Inc. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the following sponsor information page.

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1 OVERVIEW OF PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Final 1.0	21 June 2013
Final 2.0 (incorporating Protocol Amendment 1)	05 September 2013
Final 3.0 (incorporating Protocol Amendment 2)	28 January 2014
Final 4.0 (incorporating Protocol Amendment 3)	03 April 2014
Final 5.0 (incorporating Protocol Amendment 4)	05 May 2014
Final 6.0 (incorporating Protocol Amendment 5)	12 September 2014
Final 7.0 (incorporating Protocol Amendment 6)	29 May 2015
Final 8.0 (incorporating Protocol Amendment 7)	23 November 2015
Final 9.0 (incorporating Protocol Amendment 8)	17 March 2016
Final 10.0 (incorporating Protocol Amendment 9)	03 June 2016
Final 11.0 (incorporating Protocol Amendment 10)	07 July 2016
Final 12.0 (incorporating Protocol Amendment 11)	27 October 2016
Final 13.0 (incorporating Protocol Amendment 12)	22 December 2016
Final 14.0 (incorporating Protocol Amendment 13)	26 September 2017
Final 15.0 (incorporating Protocol Amendment 14)	05 October 2017
Final 16.0 (incorporating Protocol Administrative change 3)	18 July 2018

2 SUMMARY OF PROTOCOL AMENDMENTS

Fourteen amendments were made to the protocol, including 1 amendment before the first subject's first visit. A summary of key changes with each amendment is provided in Table 1.

Table 1 Protocol Amendments

Amendment Number	Date	Key Changes
1	05-Sep-2013	Revisions made in accordance with questions raised by the [redacted] Regulatory Agency and the [redacted]. Revised inclusion criterion to exclude subjects with platinum-sensitive ovarian cancer from the Expansion Part of the trial. Revised inclusion criterion to ensure that subjects with metastatic castration-resistant prostate cancer had received abiraterone and/or enzalutamide prior to entering the Expansion Part. Specified plan for assessing human anti-human antibodies to both ADC and total antibody and plan for evaluating the impact of immunogenicity on PK, activity and safety of tisotumab vedotin. Visual acuity assessment was added. Communication plan on how the assignment of subjects to a cohort was undertaken was added. Criteria for subject withdrawal from treatment were modified. A list of strong CYP3A4 inhibitors was added. Investigators were to consult an ophthalmologist for any subject experiencing clinical significant ophthalmologic AEs. Dose Escalation rules were updated. DLT definitions were updated. Details on post-infusion monitoring were added. Clarified that the CTCAE grade of all bleeding AEs were to be reported.
2	28-Jan-2014	Updated in response to the [redacted] Competent Authority request to specify the contraceptive measures, and comments from a [redacted] site Clinical Review Committee to clarify trial-related procedures and further define research endpoints.
3	03-Apr-2014	[redacted]
4	05-May-2014	[redacted]. Modified due to an event of pharyngeal tumor hemorrhage with fatal outcome. The DMC recommended exclusion of subjects with SCCHN from the Dose Escalation Part.
5	12-Sep-2014	Revised inclusion criterion no. 7 with respect to coagulation status.
6	29-May-2015	Trial phase changed from I to I/II to reflect that only the Dose Escalation Part was FIH, and the Expansion Part was phase II. Updated the Expansion Part of the trial including clarification of the approach for the types of cancers that were included, and an increase of subjects to be enrolled.
7	23-Nov-2015	Updated to encompass adaptive changes based on biomarker-derived data. Prespecified 2 of the trial cohorts for Expansion Part, endometrial and cervical cancer. Increased the planned number of subjects in the Expansion Part. Aligned the treatment guidelines in the US and EU.

Amendment Number	Date	Key Changes
8	17-Mar-2016	In order to better describe safety and preliminary biological activity signals, a cap on previous exposure to anticancer therapies for subjects to be included in the Expansion Part was introduced in this amendment. Requirements for tumor biopsies in the Expansion Part were changed so archived samples, if available, could be used. Pregnancy tests were added for women of childbearing potential in accordance with the "Recommendations related to contraception and pregnancy testing in clinical trials" of the Clinical Trial Facilitation Group.
9	03-Jun-2016	Protocol Amendment 9 was submitted to the [redacted] in response to specific questions raised during the initial trial review. In other regions Amendment 9 has been immediately superseded by the Protocol Amendment 10. Changes to Protocol Amendment 9 were made to: Clarified that the sponsor made every effort to ensure that the principles of GCP will be set in place for the exploratory analysis of protein biomarkers; specify the defined limit for human exposure of tisotumab vedotin and free toxin MMAE; clarify that all investigators received the suspected unexpected serious adverse reaction reports; explain that in case of potential serious breach, these will be reported to the competent authorities immediately.
10	07-Jul-2016	Updated with safety information concerning ocular events (conjunctivitis). Inclusion criterion on acceptable hematological status was modified. A 40-day wash-out period combined with a requirement for no residual check-point related symptoms of autoimmune toxicity was added.
11	27-Oct-2016	Modified the evaluation and mitigation plan for ocular events Some inclusion and exclusion criteria were reworded for clarification and/or to adapt to current experience or standard practice. In the Expansion Part the wording was modified regarding the number of subjects per cohort (fixed at 14 subjects) and the conditions to expand to 30 subjects to maintain flexibility to expand the cohorts with the most promising benefit/risk ratios. The number of participating sites for the Expansion Part was increased.
12	22-Dec-2016	[redacted]. One CTCAE grade 3 event of conjunctivitis had already been reported in the GEN702 trial. Following the cutoff date of 31 May 2016, 3 additional CTCAE grade 3 events of conjunctivitis and one CTCAE grade 4 event of keratitis had been reported. The purpose of the amendment was to update ~~this information in the protocol and~~ to modify the dose modification and mitigation plans for ocular events accordingly, including mandatory preventive eye therapy.
13	26-Sep-2017	Modified to allow recruitment of up to 25 additional subjects with cervical cancer for a maximum of approximately 55 subjects, updated the clinical experience and risks to human subjects based on relevant experience in ongoing trials, and clarified the evaluation and mitigation plan for ocular events.
14	05-Oct-2017	Modified the inclusion/exclusion criteria to allow subjects on stable doses of anticoagulation therapy for ≥8 weeks to enter the trial.

3 REDACTED PROTOCOL VERSION 16.0, LATEST VERSION

FIRST-IN-HUMAN, DOSE-ESCALATING SAFETY STUDY OF TISSUE FACTOR SPECIFIC ANTIBODY DRUG CONJUGATE TISOTUMAB VEDOTIN (HUMAX®-TF-ADC) IN PATIENTS WITH LOCALLY ADVANCED AND/OR METASTATIC SOLID TUMORS KNOWN TO EXPRESS TISSUE FACTOR

Investigational Product: **Tisotumab Vedotin (HuMax®-TF-ADC)**

Protocol Number: GEN701 **IND/EudraCT number:** 2013-001074-15

Study Name: innovaTV 201

Study Phase: I/II

Version and Date: Final 1.0, 21 June 2013
Final 2.0 (incorporating Protocol Amendment 1), 05 September 2013
Final 3.0 (incorporating Protocol Amendment 2), 28 January 2014
Final 4.0 (incorporating Protocol Amendment 3), 03 April 2014
Final 5.0 (incorporating Protocol Amendment 4), 05 May 2014
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Final 14.0 (incorporating Protocol Amendment 13), 26 September 2017
Final 15.0 (incorporating Protocol Amendment 14), 05 October 2017
Final 16.0 (incorporating Protocol Administrative change 3)18 July 2018

Sponsor:
Genmab A/S
Kalvebod Brygge 43
DK-1560 Copenhagen V
Denmark

Sponsor Medical Officer: [redacted]

Clinical Research Organization (CRO): [redacted]
United Kingdom

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

SIGNATURES

Sponsor Approval

Protocol: GEN701 (innovaTV 201), Version 16.0 Incorporating Administrative change 3 (18 July 2018)

Protocol Title: First-in-human, dose-escalating safety study of tissue factor specific antibody drug conjugate tisotumab vedotin (HuMax®-TF-ADC) in patients with locally advanced and/or metastatic solid tumors known to express tissue factor

[redacted]
Name

Vice President, Medical
Title

Sig[redacted]

Date [redacted]

Coordinating Investigator

I have read and agree to the protocol GEN701 (innovaTV 201), entitled 'First-in-human, dose-escalating safety study of tissue factor specific antibody drug conjugate tisotumab vedotin (HuMax®-TF-ADC) in patients with locally advanced and/or metastatic solid tumors known to express tissue factor', Version 16.0 Incorporating Administrative change 3 (18 July 2018). I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Coordinating Investigator Signature:

[redacted]
Name

Professor Section of Medicine
Institute of Cancer Research
Title

[redacted]/United Kingdom
In

Si [redacted]

Date [redacted]

1. SYNOPSIS

NAME OF SPONSOR: Genmab A/S	**PROTOCOL No.:** GEN701 STUDY NAME: innovaTV 201
NAME OF STUDY TREATMENT: Tisotumab vedotin (HuMax®-TF-ADC)	
TITLE OF STUDY: First-in-human, dose-escalating safety study of tissue factor specific antibody drug conjugate tisotumab vedotin (HuMax®-TF-ADC) in patients with locally advanced and/or metastatic solid tumors known to express tissue factor	
STUDY CENTERS: The Dose Escalation part is planned to be performed in a maximum of five sites in Denmark, United Kingdom and the United States (US), with up to 30 additional sites to be included in Europe and the US for the Cohort Expansion part.	
STUDY PERIOD: A Dose Escalation part will be followed by a Cohort Expansion part. The study will be stopped when the last patient included in the Cohort Expansion part completes the study or when the last ongoing patient has discontinued treatment and attended the Safety Follow-up Visit, whichever occurs first.	**PHASE OF DEVELOPMENT:** Phase I/II
PLANNED STUDY DATES: Enrolment period in the Dose Escalation part is planned to last approximately 21 months. Enrolment period in the Cohort Expansion part is planned to last approximately 30 months.	

OBJECTIVES:

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

Secondary Objective(s):

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

STUDY DESIGN AND METHODOLOGY:

This is a dose-escalating, open-label, multicenter phase I/II safety study of tisotumab vedotin (HuMax-TF-ADC) in a mixed population of patients with solid tumors known to express tissue factor (TF) and where the use of systemically administered tubulin inhibitors is part of standard of care (SoC). The study consists of two parts: a Dose Escalation part followed by a Cohort Expansion part. The Dose Escalation part is considered first in human and the Cohort Expansion part a phase II. A Data Monitoring Committee (DMC) will evaluate safety data during the study. The Dose Escalation part is a standard 3 (+3) design. In each dose cohort, the initial three patients must include at least two different cancer types. A maximum of eight dose levels is anticipated (not including potential intermediate dose cohorts). The Cohort Expansion part will enroll approximately 169 patients who will be treated with a regimen based on the data obtained from the Dose Escalation part. The aim of the Cohort Expansion part is to provide further safety, tolerability, PK and anti-tumor activity data from patients with cancer types that express TF. Recruitment will be initiated in five arms. Based on a safety review of data from the first ten patients recruited and followed for at least one cycle (regardless of indication), the DMC and an internal sponsor's Safety committee will evaluate the safety profile and, if deemed safe, the DMC and the sponsor's Safety committee will approve the recruitment of the three remaining arms, esophagus, non-small cell lung cancer

(NSCLC), and squamous cell carcinoma of the head and neck (SCCHN). A minimum of 14 and maximum of 30 patients will be recruited each to the cervix and endometrial indications (if one of these two indications does not appear promising while another indication shows promising efficacy, it may be decided to expand this other indication instead). After implementation of Protocol Amendment 13 (Protocol version 14.0), up to 25 additional patients will be recruited to the cervix indication, for a maximum of approximately 55 patients. In the remaining indications (ovary, bladder, castration-resistant prostate cancer [CRPC], NSCLC, esophagus and SCCHN), 14 patients will be recruited.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

The patient population in the Dose Escalation part will encompass patients with advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophagus or lung (NSCLC) who have failed available standard treatments or who are not candidates for standard therapy.

The patient population in the Cohort Expansion part will encompass patients with advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophagus, NSCLC SCCHN who have failed available standard treatments as specified in the inclusion criteria.

Patients cannot be enrolled before all inclusion criteria (including test results) are confirmed.

Inclusion Criteria:

- For the Dose Escalation part: Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, or NSCLC who have failed available standard treatments or who are not candidates for standard therapy.

For the Cohort Expansion part: Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, head and neck (SCCHN), esophagus or lung (NSCLC) who have failed the following anti-cancer therapy:

- Bladder cancer (including urothelial carcinomas [transitional cell carcinomas] regardless of the initial site of origin of the tumor: renal pelvis, ureter or bladder lumen): failing platinum-based therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
- CRPC: failing docetaxel and either abiraterone OR enzalutamide. Patients must have received no more than two prior chemotherapy-based regimens and a maximum of six prior treatment regimens for advanced disease.
- Ovarian cancer: resistant to at least one platinum-based therapy and after failing at least one line of taxane-containing therapy (isolated CA 125 progression does NOT qualify for study entry). Patients with primary platinum refractory disease are excluded. Patients must have received no more than five prior treatment regimens for advanced disease.
- Cervical cancer: failing a platinum-based regimen. Patients must have received no more than four prior treatment regimens for advanced disease.
- Endometrial cancer: failing platinum-based therapy. Patients must have received no more than four prior treatment regimens for advanced disease (excluding adjuvant chemotherapy).
- Esophageal cancer (esophageal cancer or gastro-esophageal junction (GEJ) cancer): failing platinum-based therapy with or without taxanes depending on established SoC therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
- NSCLC: failing at least one platinum-based regimen. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations should have been treated with appropriate targeted therapy before study entry. Patients must have received no more than four (five allowed for patients with EGFR mutated adenocarcinomas) prior treatment regimens for advanced disease.
- SCCHN: refractory to platinum-based therapy, also failing an anti-EGFR-based therapy if patient is eligible and if anti-EGFR therapy is part of the established SoC therapy. Patients must have received no more than one prior platinum-based and in total three prior treatment regimens for advanced disease.

- Patients must have measurable disease according to RECIST (Response Evaluation Criteria In Solid Tumors) version. 1.1. A minimum of one lesion ≥ 10 mm in the longest diameter from a non-irradiated area; lymph nodes lesion ≥ 15 mm in the shortest diameter from a non-irradiated area. Patients with prostate cancer must be clinically refractory and resistant to hormone therapy as documented by progression (CRPC) and can be included based on prostate specific antigen (PSA) and/or bone metastases according to the Prostate Cancer Working Group Guideline. Patients with ovarian cancer can be included based on CA 125 positivity according to the Gynecologic Cancer Intergroup Guideline in the Dose Escalation part only.
- Age ≥ 18 years.
- Acceptable renal function: Glomerular filtration rate (Cockcroft-Gault) > 45 mL/ min.
- Acceptable liver function: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN) (if liver tumor/ metastases are present, then ≤ 5 × ULN is allowed); bilirubin ≤ 1.5 × ULN, except in patients diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN.
- Acceptable hematological status (hematologic support is allowed if administered at least one week before Cycle 1 Day 1): hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL), absolute neutrophil count (ANC) ≥ 1500/µL (1.5×10^9/L); platelet count ≥ 100×10^9/L.
- Acceptable coagulation status: International normalized ratio (INR) ≤ 1.2 (without anticoagulant therapy), and activated partial thromboplastin time (aPTT) ≤ 1.25 ULN; patients on stable doses of therapeutic anti-coagulative treatment for ≥ 8 weeks (e.g., warfarin) must have an INR ≤ 3.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Life expectancy of at least three months.
- A negative serum pregnancy test (if female and aged between 18-55 years old). Women who are pregnant or breast feeding are not to be included.
- Patients, both females and males, of reproductive potential must agree to use adequate contraception during and for six months after the last infusion of tisotumab vedotin (HuMax-TF-ADC). Adequate contraception for women is defined as hormonal birth control or an intrauterine device. In countries where two highly effective methods of contraception are required this will be an inclusion criterion. Male patients must be willing to use a latex condom during any sexual contact with females of childbearing potential during and for six months after the last infusion of tisotumab vedotin (HuMax-TF-ADC), even after having undergone a successful vasectomy. It is recommended that fertile males consider having semen specimen obtained for storage for potential future conception.
- Following receipt of verbal and written information about the study, patients must provide signed informed consent before any study-related activity is carried out.

Key Exclusion Criteria:

- Hematological: known past or current coagulation defects leading to an increased risk of bleeding; diffuse alveolar hemorrhage from vasculitis; known bleeding diathesis; ongoing major bleeding; trauma with increased risk of life-threatening bleeding or history of severe head trauma or intracranial surgery within two months of study entry.
- Cardiovascular: clinically significant cardiac disease (including unstable angina, acute myocardial infarction within six months of the Screening Visit, known congestive heart failure [Grade III or IV as classified by the New York Heart Association], and/ or a known decreased cardiac ejection fraction of < 45%); a baseline QT interval as corrected by Fridericia's formula (QTcF) > 450 msec, a complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form) or an incomplete left bundle branch block.
- Excluded medications or treatment regimens: have received granulocyte colony stimulating factor

(G-CSF) or granulocyte/macrophage colony stimulating factor support within one week or pegylated G-CSF within two weeks before the Screening Visit; have received a cumulative dose of corticosteroid ≥ 150 mg (prednisone, or equivalent doses of corticosteroids) within two weeks before the first infusion.

- Surgery/procedures: major surgery within six weeks or open biopsy within seven days before drug infusion; plan for any major surgery during treatment period; patients not willing or able to have a pre-study tumor biopsy taken (in the Dose Escalation part the screening biopsy can be omitted if archived material is available; in the Cohort Expansion part the most recent available archived sample can be used, if no biopsies are available a new biopsy must be obtained before dosing); presence or anticipated requirement of epidural catheter in relation to infusions (within 48 hours before and after dose of study drug).
- Central nervous system: any history of intracerebral arteriovenous malformation, cerebral aneurysm, brain metastases or stroke (transient ischemic attack > 1 month prior to screening is allowed).
- Prior therapy: any anti-cancer therapy including; small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug within five half-lives before first infusion (for anti-cancer therapies with half-lives > 8 days, a washout period of at least 28 days is acceptable); prior treatment with bevacizumab within twelve weeks before the first infusion; any prior therapy with a conjugated or unconjugated auristatin derivative; radiotherapy within 28 days prior to first dose; patients who have not recovered from symptomatic side effects of radiotherapy or symptoms of autoimmune toxicities related to previous treatment with check-point inhibitors at the time of initiation of screening procedure.
- Other cancer/metastases: known past or current malignancy other than inclusion diagnosis, except for: cervical carcinoma of Stage 1B or less; non-invasive basal cell or squamous cell skin carcinoma; non-invasive, superficial bladder cancer; prostate cancer with a current PSA level < 0.1 ng/mL; breast cancer in BRCA1 or BRCA2 positive ovarian cancer patients; or any curable cancer with a complete response (CR) of > 5 years duration. Radiographic evidence of cavitating pulmonary lesions. Tumor adjacent to (Dose Escalation part only) or invading (both parts) any large blood vessel, unless approved by the sponsor Medical Officer should also be excluded.
- Other: ongoing significant, uncontrolled medical condition; presence of CTCAE (Common Toxicity Criteria for Adverse Events) grade ≥ 2 peripheral neuropathy; clinically significant active viral, bacterial or fungal infection requiring intravenous treatment with antimicrobial therapy starting less than four weeks prior to first dose or oral treatment with antimicrobial therapy starting less than 10 days prior to first dose; known human immunodeficiency virus seropositivity; positive serology (unless due to vaccination or passive immunization due to Ig therapy) for hepatitis B defined by positive test for HBsAg (hepatitis B surface antigen) and/or positive test for anti-HBs and anti-HBc (antibodies to hepatitis B surface and core antigens); positive serology for hepatitis C based on test at screening; inflammatory bowel disease including Crohn's disease and colitis ulcerosa; inflammatory lung disease including moderate and severe asthma and chronic obstructive pulmonary disease (COPD) requiring chronic medical therapy; ongoing acute or chronic inflammatory skin disease.
- Ophthalmological: active ocular surface disease at baseline (based on ophthalmological evaluation); history of cicatricial conjunctivitis (as evaluated by an ophthalmologist).

NUMBER OF SUBJECTS: Approximately 310 patients will be screened to ensure that up to 217 patients (anticipated screen failure rate of 30%) are enrolled in the study.

A maximum of 48 patients are planned to be enrolled in the Dose Escalation part: three to six patients per dose level for eight dose levels. Approximately 169 patients will be enrolled in the Cohort Expansion part.

STUDY TREATMENT(S): In the Dose Escalation part, tisotumab vedotin (HuMax-TF-ADC) will be administered as an intravenous infusion over one hour on Day 1 of each cycle; in the Cohort Expansion part, tisotumab vedotin (HuMax-TF-ADC) will be administered as an intravenous infusion over 30 minutes on Day 1 of each (1 treatment cycle is 21 days). Preventive eye therapy should be administered in relation

to infusions.

The Dose Escalation part is a standard 3 (+3) design which will evaluate tisotumab vedotin (HuMax-TF-ADC) at doses of 0.30 mg/kg and up (0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.2 and 2.6 mg/kg). The maximum tested dose will be 2.6 mg/kg. Decisions to escalate the dose of tisotumab vedotin (HuMax-TF-ADC) for the next cohort will be based on the safety data obtained from the 3 (+3) patients during their first treatment cycle (21 days). A DMC will evaluate all safety data (including serious adverse events [SAEs], adverse events [AEs], and laboratory data) after each cohort completes Cycle 1. The DMC and the sponsor's Safety committee will, based on the Dose Escalation part, determine the dose level to be used in the Cohort Expansion part. At the conclusion of the Dose Escalation part, the dose level selected for the Cohort Expansion part is 2.0 mg/kg. 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.

DURATION OF TREATMENT: In the Dose Escalation part, the patients will be treated for four cycles or until unacceptable toxicity. After four cycles, if there is evidence of the patient benefitting from treatment, at the discretion of the treating physician after agreement with Genmab on the patient status, there is an option to continue in the study for up to a maximum of eight additional cycles (24 weeks) or until unacceptable toxicity according to protocol is observed. The treatment period will have a maximum duration of 36 weeks.

In the Cohort Expansion part, the patients will be treated with the dose identified from the Dose Escalation part by the DMC and the sponsor's Safety committee for four cycles or until unacceptable toxicity. After four cycles, if there is evidence of the patient benefitting from treatment, at the discretion of the treating physician, there is an option to continue in the study for up to a maximum of eight additional cycles (24 weeks) or until unacceptable toxicity is observed. The treatment period will have a maximum duration of 36 weeks.

At the end of the planned number of cycles in both parts, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as stable disease (SD) or better, until unacceptable toxicity or Progressive Disease (PD) is observed.

STUDY EVALUATIONS:

Primary Endpoint:

- AEs during the study: incidences of AEs, SAEs, infusion-related AEs, CTCAE grade ≥ 3 AEs, and AEs related to study drug.

Secondary Endpoints:

- Safety laboratory parameters (hematology, biochemistry, coagulation factors and flow cytometry).
- Skin disorders.
- Bleeding events.
- Neuropathy.
- PK parameters (clearance, volume of distribution and area-under-the-concentration-time curve [$AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$]), maximum concentration [C_{max}], time of C_{max} [T_{max}], pre-dose values, and half-life of tisotumab vedotin (HuMax-TF-ADC) and free toxin [MMAE]).
- Immunogenicity (anti-drug antibodies) of tisotumab vedotin (HuMax-TF-ADC).
- Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT] scan evaluations), change in PSA and CA 125.
- Objective Response (CR or Partial Response [PR]), Disease Control (CR, PR or SD) after 6, 12, 24 and 36 weeks, Progression-Free Survival (PFS) and Duration of Response (DoR).

Exploratory Endpoints:

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

STATISTICAL METHODS: The presentations will be done separately for the Dose Escalation and Cohort Expansion parts. No formal statistical tests will be performed: descriptive statistics will be presented. Two-sided 95% confidence intervals will also be calculated. All data will be listed.

The full analysis population will comprise all patients who have been exposed to study drug and will be used for evaluation of all endpoints.

Further details will be given in a separate Statistical Analysis Plan.

DATE AND VERSION: Final 16.0 incorporating Protocol Administrative change 3, 18 July 2018

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
3q4w	Three times every four weeks
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area-under-the-concentration-time curve
BMI	Body mass index
BSA	Body surface area
cfDNA	Cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CR	Complete Response
CRO	Clinical research organization
CRPC	Castration-resistant prostate cancer
CT	Computerized tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EOS	End of Study
FVII, FIX, FX	Factor VII, factor IX, factor X

FVIIa, FIXa, FXa	Activated factor VII/factor IX/factor X
FDA	Food and Drug Administration
FIH	First-in-human
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GEJ	Gastro-esophageal junction
GI	Gastrointestinal
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HNSTD	Highest non-severely toxic dose
HPV	Human papilloma virus
HuMax®-TF-ADC	HuMax tissue factor antibody drug conjugate (tisotumab vedotin)
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Independent Review Board
IRR	Infusion-related reaction
LD	Longest Diameter
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
PAR-2	Protease activated receptor 2
PCR	Polymerase chain reaction
PD	Progressive disease

PFS	Progression-Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial Response
PSA	Prostate specific antigen
PT	Prothrombin time
q3wk	Every three weeks
qRT-PCR	real-time quantitative polymerase chain reaction
QTcF	QT interval as corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase II dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable Disease
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEG	Thromboelastography
TEN	Toxic Epidermal Necrolysis
TF	Tissue factor
TMA	Tissue microarray
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
US/USA	United States/United States of America
Vc	Valine citrulline
VEGF	Vascular endothelial growth factor
WMA	World Medical Association

4. ETHICS

4.1 Ethics Committee

This study will be conducted in compliance with independent ethics committee (IEC)/institutional review board (IRB) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the United States of America (USA) Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the United States Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312), in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). In addition this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the investigator/institution must have written and dated approval/favorable opinion from the IEC/IRB for the study protocol/amendment(s), written Informed Consent Form (ICF), any consent form updates, patient recruitment procedures (e.g., advertisements), and any written information to be provided to patients and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R2); FDA CFR (21 CFR § 50, 56, 312)), Declaration of Helsinki (Fortaleza 2013) (Appendix 3) and all applicable regulatory requirements.

It is possible that the exploratory endpoint analysis of protein biomarkers may not fulfill the above GCP compliance statement. Best efforts to make sure that the research laboratory follows the principles of GCP will be set in place.

4.3 Patient Information and Consent

The investigator will explain the benefits and risks of participation in the study to each patient and will obtain written informed consent. Written informed consent must be obtained prior to the patient entering the study and before initiation of any study-related procedure (including administration of study drug).

The IEC/IRB-approved information and consent form that is used must be in language readily understood by the patient. Each patient's original consent form, personally signed and dated by the patient and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled patients with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety and procedures of the patient. In this

instance approval should always be given by the IEC/IRB and existing patients informed of the changes and reconsented. This is documented in the same way as previously described.

The investigator should, with the consent of the patient, inform the patient's primary physician about participation in the clinical study.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

International Coordinating Investigator:
The Dose Escalation part of the study will be performed in a maximum of five phase I units in Denmark, United Kingdom and USA. For the Cohort Expansion part of the study there will be up to 30 additional sites in Europe and the US. The Coordination Investigator will be:

[redacted] UK

A Data Monitoring Committee (DMC) will be established. Refer to Section 11.5.

For the Dose Escalation part, central laboratories will be used for the analysis of flow cytometry, pharmacokinetics (PK), immunogenicity, and protein-based biomarkers. For the Cohort Expansion part, all blood samples will be analyzed at a Central Laboratory. Details of the central laboratories and handling of samples will be provided in a separate study manual.

Central facilities will be used for scan reading (for the Cohort Expansion part only) and for electrocardiogram (ECG) reading. Details of the central facilities and shipping instructions will be provided in a separate study manual.

Investigational Medicinal Product (IMP) will be supplied by [redacted], Denmark, [redacted], Denmark, [redacted].

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6. INTRODUCTION

6.1 Key Background and Rationale

Tisotumab vedotin (HuMax®-TF-ADC) is an antibody drug conjugate (ADC) composed of a human monoclonal immunoglobulin G1 ([IgG1] subtype κ) targeting tissue factor (TF; HuMax-TF) conjugated via a protease cleavable valine citrulline (vc) linker to the drug monomethyl auristatin E (MMAE), a dolastatin 10 analog (Doronina et al., 2003; Hamblett et al., 2004; Sun et al., 2005). Dolastatins and auristatins belong to a class of chemotherapies that act as microtubule disrupting agents.

Human TF (thromboplastin, CD142 or coagulation factor III) is a 43-47 kDa, single chain, transmembrane glycoprotein. TF is the main initiator of the extrinsic pathway of blood coagulation, which starts when TF binds to serine protease factor VII (FVII) or activated FVIIa. The TF:FVIIa complex initiates blood coagulation by proteolytic cleavage of factor X (FX) to FXa, and factor IX (FIX) to FIXa, eventually leading to thrombin generation and the formation of a clot. In addition, the TF:FVIIa complex can initiate an intracellular signaling cascade by proteolytic activation of protease activated receptor 2 (PAR-2), resulting in release of pro-angiogenic factors and pro-inflammatory mediators such as vascular endothelial growth factor (VEGF) and interleukin-8.

Under pathological conditions, membranous TF can be aberrantly expressed. TF is present on neoplastic cells as well as tumor-associated endothelial cells in a variety of solid cancers. Indications where tumor cells are known to express TF include gynecological and genito-urethral tumors, squamous cell carcinoma of head and neck (SCCHN), lung cancers, tumors in the gastrointestinal (GI) tract, breast cancer, malignant melanoma and pancreatic cancer (Ohta et al., 2002; Akashi et al., 2003; Khorana et al., 2007; Uno et al., 2007; Patry et al., 2008; Yokota et al., 2009; Cocco et al., 2011). For most of these indications, high TF expression in tumor biopsies was confirmed using in house immunohistochemistry (IHC) studies. However, the high incidence of TF-positive tumors that was previously described in breast cancer and malignant melanoma could not be confirmed. To select the indications to be included in tisotumab vedotin (HuMax-TF-ADC) first-in-human (FIH) clinical study, significant expression of the target (TF) in tumor biopsy material as well as thorough information on efficacy of tubulin inhibition as part of standard of care (SoC) were used as selection criteria. The indications to be included in this FIH study are gynecological (ovarian, endometrial and cervical), genito-urethral (bladder and castration-resistant prostate [CRPC]), head and neck (SCCHN), esophagus and non-small cell lung cancer (NSCLC) cancers. In these indications, TF expression is variable and IHC data derived from the literature and Genmab studies have shown TF expression in up to 75%-100% of the tumors (Akashi et al., 2003; Chen et al., 2010; Cocco et al., 2010; Cocco et al., 2011a; Cocco et al., 2011b; Patry et al., 2008; Sawada et al., 1999; Uno et al., 2007; Yao et al., 2009; Wojtukiewicz et al., 1999).

Expression of TF on tumor cells has been associated with negative overall survival or disease free survival as described in several indications, including ovarian, bladder and pancreatic cancer (Nitori et al., 2005; Han et al., 2006; Patry et al., 2008). Experimental studies suggest that tumor cells may benefit from both TF procoagulant activity and TF-induced PAR-2

signaling, for example through enhanced metastatic potential, angiogenesis and cell survival (Ruf and Mueller, 1996; Kasthuri et al., 2009). Furthermore, monoclonal antibodies that inhibited either TF:FVIIa intracellular signaling or TF procoagulant capacity could reduce tumor growth *in vivo* (Versteeg et al., 2008).

Constitutive TF expression is mostly restricted to sub endothelial cells (such as pericytes, smooth muscle cells and fibroblasts,) that only interact with blood borne FVIIa when vascular integrity is compromised (Drake et al., 1989). TF is expressed in the vessel walls of a wide range of organs, with moderate to high levels observed in the brain, heart, intestine, kidney, lung, placenta, uterus, and testes. The expression pattern suggests that TF provides additional hemostatic protection to these organs. In addition, TF expression has been described in epithelial cells in a number of organs including the skin, kidney and lung (Flössel al., 1994; Drake et al., 1989; Imokawa et al., 1997). Under pathological, inflammatory conditions TF is aberrantly expressed, including but not limited to bullous pemphigoid, urticaria (primarily on eosinophils, Marzano et al., 2009; Marzano et al., 2011; Cugno et al., 2009), inflammatory GI diseases including Crohn's disease and ulcerative colitis (More et al., 1993) and lung diseases including acute respiratory distress syndrome (Bastarache et al., 2007).

Broad expression of TF was confirmed in a tissue cross-reactivity study. Binding of HuMax-TF-ADC was observed on e.g. epithelial cells in organs, including but not limited to skin, breast, lungs, GI tract, kidney, liver and eye. Staining in glomeruli, islet cells in pancreas, peripheral nerves, cardiomyocytes, smooth myocytes (esophagus, stomach and prostate) and processes of glial cells in grey matter was also observed [redacted].

In the clinic, systemic tubulin inhibitors are used in many indications within solid tumor oncology, approved by authorities or used as part of SoC. Indications include cancer of the ovaries, endometrium, cervix, bladder, prostate, esophagus, stomach, head and neck (SCCHN), breast, and NSCLC, all of which are described to express TF.

HuMax-TF-ADC shows excellent anti-tumor activity *in vitro* and *in vivo*. Efficient tumor cell killing is thought to rely on HuMax-TF-ADC binding to TF on the cell surface of tumor cells followed by rapid internalization and lysosomal processing of MMAE (GMB1015-087 available upon request). Subsequent intracellular release of MMAE results in tumor cell killing by disruption of the microtubule network. In addition, MMAE can exert so-called bystander toxicity by diffusion to neighboring tumor cells or tumor stromal cells. The cytotoxic effect mediated via MMAE release in target cells is believed to be the main mechanism of action of HuMax-TF-ADC. *In vitro* studies demonstrated that HuMax-TF-ADC and unconjugated HuMax-TF also induce antibody-dependent, cell-mediated cytotoxicity and inhibition of TF:FVIIa signaling. The contribution of these mechanisms to tumor cell killing remains unknown.

Despite efficient TF binding, HuMax-TF-ADC and unconjugated HuMax-TF showed minimal interference with TF procoagulant activity *in vitro* and *in vivo*, as was previously described for other TF-specific antibodies (unpublished data; Kirchhofer et al., 2000; Versteeg et al., 2008). Thus, HuMax-TF-ADC provides efficient targeting of TF-positive tumor cells, without a major impact on coagulation.

In summary, HuMax-TF-ADC is an attractive molecule for anti-cancer therapy in solid tumors.

Based on known TF expression and usage of tubulin inhibition as part of treatment paradigms, indications to be included in the FIH clinical study of HuMax-TF-ADC encompass ovarian, endometrial, cervical, prostate (CRPC), bladder, NSCLC, esophageal and SCCHN carcinomas.

6.1.1 Rationale for Indications

6.1.1.1 Selected Indications

To select the indications to be included in this tisotumab vedotin (HuMax-TF-ADC) FIH clinical study, significant expression of the target (TF) as well as thorough information on efficacy of tubulin inhibition as part of SoC were used as selection criteria.

Tissue factor is a transmembrane glycoprotein, aberrantly expressed under pathological conditions. Tissue factor has been described on neoplastic cells as well as tumor-associated endothelial cells in a variety of solid cancers. Indications where tumor cells are known to express TF include, but are not limited to, gynecological and genito-urethral tumors, SCCHN, lung cancers and tumors in the GI tract (Ohta et al., 2002; Akashi et al., 2003; Khorana et al., 2007; Uno et al., 2007; Patry et al., 2008; Yokota et al., 2009; Cocco et al., 2011). Knowledge about expression of TF mostly derives from IHC staining. In this section, available data on TF expression derived from literature, as well as results on a study of TF expression and incidence in multiple tumor tissue micro arrays performed by Genmab (Study report: SR1015-091) are summarized below. Information on indications is derived from the Cancer Facts & Figures 2012, SEER database, combined with the advice of key opinion leaders. Treatment algorithms involving tubulin inhibition are obtained from the National Comprehensive Cancer Network (NCCN) guidelines.

Indications to be included in the FIH clinical study of tisotumab vedotin (HuMax-TF-ADC) encompass ovarian, endometrial, cervical, prostate (CRPC), bladder, NSCLC, esophageal and SCCHN carcinomas.

The DMC has recommended the exclusion of patients with SCCHN carcinomas in the Dose Escalation part of the study due to an event of pharyngeal tumor hemorrhage with fatal outcome in the 0.6 mg/kg cohort. The DMC underlined that the event was most likely related to the disease itself and the natural course of disease for some of these patients; however, a causal relationship cannot be completely excluded, and further experience from other tumors is to be warranted before re-exposure to this cancer type. SCCHN carcinomas have therefore been removed from the Dose Escalation phase with the implementation of Amendment 4.

6.1.1.2 Gynecological cancers

In gynecological tumors, TF expression has been described predominantly in ovarian, endometrial as well as cervical cancers.

6.1.1.2.1 Ovarian Cancer

In US, 22,000 new cases and 15,500 deaths are estimated each year. Approximately 70% of patients will manifest with advanced disease, and five year survival is reported to be 30-40%

for stage III, decreasing to 20% for stage IV. As frontline chemotherapy for treatment of advanced disease, tubulin inhibition is used in combination with cisplatin. Tubulin inhibition is also used as second line in the platin resistant population as well as in later lines of therapy. In ovarian cancer, Uno et al reported expression of TF in 31 of 36 (86%) consecutive patients. In this paper, correlation with high TF expression and venous thromboembolism was indicated (Uno et al., 2007). Cocco et al reported TF expression in 24 of 25 (96%) ovarian cancer samples tested and no positive staining in normal ovarian tissue; these data were further supported by increased expression in tumor cell lines analyzed by real-time quantitative polymerase chain reaction (qRT-PCR, Cocco et al., 2011b). In report SR1015-091, 40% of the tested samples were found to be positive for TF expression.

6.1.1.2.2 Endometrial Cancer

In US, 47,000 new cases and 8,000 deaths are estimated each year. Approximately 33% of patients manifest with advanced disease, and five year survival is reported to be 47-58% for stage III, decreasing to 15-17% for stage IV. As frontline chemotherapy treatment, tubulin inhibition is used in combination with platin and also as single agent therapy in a relapsed setting. In endometrium cancer, Cocco et al reported cytoplasmatic and/or membranous staining in all tumor samples tested by IHC (n=16); these findings were supported by increased mRNA expression in all six endometrial tumor derived cell lines tested (Cocco et al., 2010). In report SR-1015-003, positive staining for TF expression was found in 59% of the tested samples.

6.1.1.2.3 Cervical Cancer

In US, 12,000 new cases and 4,200 deaths are estimated each year. Approximately 50% of patients manifest with advanced disease; however, this figure might decrease with availability of human papilloma virus (HPV) screening programs. Anticipated five year survival is reported to be approximately 40% for stage III, decreasing to 15% for stage IV. As frontline chemotherapy treatment, tubulin inhibition is used in combination with platin and also as single agent therapy in a relapsed setting. For cervical cancers, Cocco et al reported positive staining in eight of eight tumor samples analyzed as well as increased expression detected by qRT-PCR in 11 of 11 cervical carcinoma cell lines tested (Cocco et al., 2011a). In report SR1015-091, 86% of the tested tumor samples were found positive for TF expression.

6.1.1.3 Genito-urethral Cancers

In genito-urethral tumors, TF expression has been described predominantly in cancers of the prostate and bladder.

6.1.1.3.1 Prostate Cancer (Metastatic, CRPC)

In US, 241,000 new cases and 28,200 deaths are estimated each year. Approximately 10-20% of patients manifest with advanced disease. For metastatic disease, an estimated survival of 24-36 months is reported, decreasing to 12-18 months in metastatic CRPC. In metastatic, CRPC, frontline chemotherapy includes tubulin inhibition – where docetaxel is SoC in combination with steroid. In prostate cancer, Akasi et al reported positive TF expression in 75% of tumors from 73 patients with metastatic prostate cancers (Akashi et al., 2003). These

data were consistent with those published by Abdulkadir et al, where most of the prostate carcinoma specimens examined (73%; 49 of 67 samples) were found to express high levels of TF (Abdulkadir et al., 2000). In a study analyzing archived tissue microarrays (TMAs) from both benign prostate, intraepithelial neoplasia and carcinoma, positive staining was seen predominantly in carcinoma (47% of 43 tested samples), and it was significantly lower both in intraepithelial neoplasia and in benign tissues, where only 9% of samples tested were positive for TF staining (Yao et al., 2009). In report SR1015-091, 60% of the tested tumor samples expressed TF.

6.1.1.3.2 Bladder Cancer

In US, 73,500 new cases and 14,900 deaths are estimated each year. Approximately 30% of patients manifest with advanced disease. Anticipated five year survival is reported to be approximately 40-50% for stage III, decreasing to 15% for stage IV. As frontline chemotherapy treatment, tubulin inhibition is used in combination with platin and also as single agent therapy in a relapsed setting. In muscle invasive bladder cancer, Patry et al reported positive staining for TF in 78% of TMAs obtained from 218 patients (Patry et al., 2008). In report SR1015-091, positive staining was observed in 45% of tested samples.

6.1.1.4 Lung Cancers

In lung tumors, most data on TF expression derives from NSCLC. In US, 226,000 new cases and 160,300 deaths are estimated each year. NSCLC accounts for approximately 2/3 of cases. Approximately 50-78% of patients manifest with advanced disease hereof 40% with metastatic disease. Anticipated five year survival is reported to 10-25% for stage IIIb, decreasing to 4% for stage IV. As frontline chemotherapy treatment of metastatic disease, tubulin inhibition is used in combination with cisplatin and as single agent after chemotherapy failure. Sawada et al reported positive TF expression in 84% of 55 tumor samples obtained from patients with NSCLC; of interest, more intense staining was described in patients with metastatic disease (Sawada et al., 1999). Comparable data were generated in report SR1015-091, where TF positivity was found in 62% (adenocarcinoma) and 86% (squamous cell carcinomas) of tested tumor samples, respectively.

6.1.1.5 Gastrointestinal Cancers

In GI tumors, significant TF expression is predominantly described in esophageal as well as in colorectal tumors. However, as colorectal cancer is described to be resistant to tubulin inhibition, only esophageal cancer will be described.

6.1.1.5.1 Esophageal Cancer

In US, 17,500 new cases and 15,000 deaths are estimated each year. Approximately 65% of patients manifest with advanced disease. Anticipated five year survival is reported to be 20-25% for stage III, decreasing to 4% for stage IV. Frontline chemotherapy includes tubulin inhibition in combination with platin plus 5-fluorouracil or irinotecan (mostly used in a relapsed setting). In a relapsed population, single agent tubulin inhibition can be used. In esophageal cancers, Chen et al described positive TF expression in 91% of tumors obtained from 103 patients with esophageal squamous cell carcinomas, while normal esophageal

tissue was found to be immunoreactive negative (Chen et al., 2010). No data on TF expression in esophageal cancer are available in the SR1015-091 report.

6.1.1.6 Head and Neck Cancer

Head and neck cancer comprise tumors of the nasal cavity, tongue, oral cavity, larynx and pharynx. TF expression has predominantly been described for SCCHN.

6.1.1.6.1 SCCHN

In US, 39,800 new cases and 9,500 deaths are estimated each year. Approximately 60% of patients manifest with advanced disease. Anticipated five year survival reported to be 10-40% for stage III, decreasing to 0-30% for stage IV. Patients with tumors positive for HPV seem to have a more favorable prognosis than patients with HPV negative tumors. Frontline chemotherapy contains platin. Use of tubulin inhibition has involved combination with cisplatin and 5-fluorouracil. In SCCHN, Wojtukiewicz et al reported expression of TF on SCCHN tumor cells samples from squamous cell carcinomas of the larynx obtained after surgical resection (Wojtukiewicz et al., 1999). In report SR1015-091, positive staining for TF was observed in 84% of the tested samples.

Thus, for all mentioned indications, significant information on expression of TF is available. However, it should be noted that variable TF expression has been described. Differences in methodology as well as different monoclonal antibody used for detection are likely to account for these observations. The extent of TF expression on cancer cells necessary for anti-tumor efficacy of tisotumab vedotin (HuMax-TF-ADC) *in vivo* is also unknown, and as such no cut-off limit can be enforced at present. It should be noted that TF expression on tumor vessels may also contribute to anti-tumor efficacy. Expression of TF on tumor cells has been associated with negative overall survival or disease free survival as described in several indications, including ovarian and, bladder cancer (Han et al., 2006; Patry et al., 2008). In addition, for the selected indications, systemic tubulin inhibition is part of SoC for both frontline treatment as well as treatment in relapsed patient populations with advanced and/or metastatic disease.

6.1.2 Indications for the Cohort Expansion Part

The Cohort Expansion part of the study is designed to gather additional safety, tolerability, PK, and anti-tumor activity data by exposing patients at the maximum tolerated dose (MTD) found in the Dose Escalation part or at the dose level recommended by the sponsor, in collaboration with the DMC, for further development. Approximately 169 patients will be enrolled in the Cohort Expansion part, which is considered sufficient to provide the basis for the planning and design of further studies. The Cohort Expansion part has a parallel group design, with a minimum of 14 and maximum of 30 patients in the cervix and in the endometrial indications, and 14 patients in the remaining indications (see Section 6.1.1.1). If after 14 patients treated for four cycles in the cervix or endometrial indications no responders have been observed, a DMC will evaluate whether it is reasonable to expand the particular indication up to 30 patients. If one of these two indications does not appear promising while there is another indication that shows promising efficacy, it may be decided to expand the other indication instead. After implementation of Protocol Amendment 13 (Protocol version

14.0), up to 25 additional patients will be recruited to the cervix indication for a maximum of approximately 55 patients.

Recruitment will be initiated in five arms encompassing ovary, cervix, endometrium, bladder and prostate (CRPC) cancer. Based on a safety review of data from the ten first patients recruited and followed for at least one cycle (regardless of indication), the DMC and internal sponsor's Safety committee will evaluate the safety profile with particular emphasis on coagulation status and possible cases of hemorrhages. If safety profile is deemed safe, the DMC and sponsor's Safety committee will approve the recruitment of the three remaining arms, esophageal cancer, NSCLC and SCCHN.

6.2 Compound Review

Tisotumab vedotin (HuMax-TF-ADC) is an ADC composed of a human monoclonal IgG1κ targeting TF (HuMax-TF) conjugated via a protease cleavable linker to MMAE, a dolastatin 10 analog. Dolastatins and auristatins belong to a class of chemotherapies that act as microtubule disrupting agents. Each monoclonal antibody molecule carries an average of four drug moieties.

The IMP is a powder for solution for infusion.

6.2.1 Non-Clinical Studies

Due to restricted species cross-reactivity, the only relevant species for non-clinical safety assessment of HuMax-TF and tisotumab vedotin (HuMax-TF-ADC) was the monkey.

The pre-clinical toxicity of unconjugated HuMax-TF in cynomolgus monkeys at doses up to and including 100 mg/kg showed a decrease in erythrocytes, hemoglobin, hematocrit and an increase in reticulocyte counts, assessed as probably related to blood sampling. An increase in neutrophil and leucocyte counts was observed, assessed as probably due to stress. No adverse effects on coagulation and thromboelastography (TEG) were observed. Urine tests were unaffected. There was a decrease in alkaline phosphatase and gamma-glutamyl transferase. B- and T- lymphocyte, monocyte and platelet counts were increased, whereas natural-killer cell counts decreased initially after dosing, but quickly recovered. No effect was seen on inflammatory cytokines and complement factors and Coombs test was negative. Functional bleeding time (Surgicutt™) on Day 22 was marginally increased following administration of 100 mg/kg HuMax-TF.

It was concluded that no major toxicity was observed for unconjugated HuMax-TF. A marginally prolonged bleeding time was found; however, no adverse effects on general coagulation parameters including TEG were seen.

In a pilot toxicology study in cynomolgus moneys, employing various anti-TF ADCs including HuMax-TF-ADC, dose levels up to and including 5 mg/kg were administered weekly for four cycles. Decreases in erythrocytes, hemoglobin and hematocrit, and increases in reticulocyte counts and a marked decrease in neutrophil counts were assessed as probably due to an impact of MMAE on the bone marrow. This was confirmed histopathologically by a decrease in bone marrow cellularity. High serum iron was observed. Liver and kidney examinations were normal. Urine tests were normal.

In a dose range finding study HuMax-TF-ADC was dosed at 1, 3 and 6 mg/kg once every three weeks (q3wk). Severe neutropenia in high dose animals (6 mg/kg) was observed and, in some animals, associated with clinical signs indicative of sepsis. One animal was sacrificed due to sepsis-related adverse findings, most likely arising due to the low neutrophil count. The highest dose was decreased to 5 mg/kg and prophylactic antibiotics implemented. Reddening and flaky skin was observed at 3 and 5-6 mg/kg and was most prominent after the first dose administration.

In the 3 mg/kg group, neutropenia was moderate and not associated with the clinical signs observed at 6 mg/kg. In the 1 mg/kg group, no neutropenia was observed.

It was concluded that HuMax-TF-ADC is well tolerated at doses up to and including 3 mg/kg.

In the pivotal 13-week repeat dose toxicology study, employing dose levels of 1, 3 and 5 mg/kg using a once per three-week dosing schedule, similar findings as described above were evident. Severe neutropenia was observed at 5 mg/kg, a moderate effect at 3 mg/kg and no effect at 1 mg/kg. Decreases in red cell parameters, platelets and lymphocytes were also evident occasionally and the effect was most pronounced at the high dose level. No major or consistent alterations of kidney or liver related clinical chemistry parameters were evident.

The coagulation parameters prothrombin time (PT) and activated partial thromboplastin time (aPTT) were unaffected by treatment with HuMax-TF-ADC. Occasionally, high fibrinogen concentrations were observed in some high dose animals, when compared with control and pre-study values.

High haptoglobin concentrations were observed throughout the treatment period in males and females at 5 mg/kg HuMax-TF-ADC, occasionally attaining statistical significance. Haptoglobin concentrations during the recovery period were considered similar to control and pre-study values.

Urine analysis was normal and no blood was evident in either urine or stool.

Assessment of ECG and respiratory rate did not indicate any effect of treatment.

Skin reactions were seen at both 3 and 5 mg/kg with good recovery in most animals. Due to severe skin reactions, four animals (one male and three females) in the high dose group were sacrificed based on welfare grounds. The effect on the skin may be target-related and may have been aggravated further due to a low neutrophil count and the presence of bacteria.

These skin reactions were evaluated by a dermato-pathologist who described the findings as follows: “Cutaneous toxicity occurred at about 3-9 days after first dose in the mid to high range doses (3, 4, or 5 mg/kg). These animals displayed initially flexural erythema, scaling and erosions leading to ulceration in high dose animals (4 and 5 mg/kg). Follow-up studies with biopsies at the time of initial erythema (sample obtained at Day 6-8 post-dosing) revealed basal layer vacuolization, keratinocyte dysmaturation, dyskeratosis and a superficial lymphocytic infiltrate. The findings were seen diffusely, but were most severe in clinically involved skin of the femoral and neck. Thrombosis of blood vessels and vasculitis were not seen. The histologic picture is consistent with chemotherapeutic effect as described with

multiple different chemotherapeutic agents (Cady et al., 2006; Degen et al., 2010, Chalermchai et al., 2010; Benghiat and Al-Niaimi, 2011)."

Daily assessment of vaginal smears for the monitoring of ovarian cycle did not indicate any effect of treatment with HuMax-TF-ADC on the menstrual cycle.

Following administration of HuMax-TF-ADC, once q3wk for thirteen weeks (five doses in total), histopathological changes characterized by seminiferous tubular atrophy were observed in the testis and were associated with administration of 1, 3, and 5 mg/kg of HuMax-TF-ADC. In the epididymis findings included absence of sperm/decreased sperm content and epithelial vacuolation [redacted]. At 3 and 5 mg/kg mean testes and epididymis weights were also lower compared to controls but statistical significance was not attained. Associated sperm count also tended to be reduced and sperm motility was absent or reduced in some animals at 1, 3 and 5 mg/kg. Full recovery of the testicular/epididymal findings was evident at 1 mg/kg and partial recovery was observed at 3 and 5 mg/kg HuMax-TF-ADC.

Ophthalmoscopy data, obtained during week 12 of treatment, indicated a very mild effect on the fundus, which appeared glassy, in all male monkeys at 5 mg/kg HuMax-TF-ADC and at 25 mg/kg HuMax-TF. No effects were observed after the fifth dose administration in either group. No similar effect was seen in female monkeys treated with either test item. This finding was not deemed treatment-related.

During efficacy studies in mice, high dose treatment (50 mg/kg) with unconjugated HuMax-TF induced intratumoral hemorrhages in one out of five xenograft models. Hemorrhages were not observed after treatment with a lower dose of HuMax-TF (15 mg/kg). Treatment with HuMax-TF-ADC was associated with intratumoral hemorrhages in one out of fifteen xenograft models. This particular model, NCI-H441 xenograft model, was prone to intratumoral hemorrhages even without treatment but the frequency was enhanced after treatment with 4.5 mg/kg HuMax-TF-ADC. A similar dose of HuMax-TF did not induce intratumoral hemorrhages. It was concluded that the occurrence of intra-tumoral hemorrhages upon treatment with HuMax-TF or HuMax-TF-ADC is rare, and largely related to the inherent characteristics of the tumor model. At dose levels relevant for ADCs, antibody-mediated interference with TF function was not associated with intratumoral hemorrhages, although the toxin part of the ADC may induce intratumoral hemorrhages in xenograft models that are prone to bleeding.

The safety monitoring for the FIH study of HuMax-TF-ADC will be based on the pre-clinical findings, the class effects of the anti-microtubule agent MMAE and experience with other anti-TF-antibodies.

Further information can be found in the Investigator's Brochure.

6.2.2 Previous Clinical Experience with MMAE-based ADCs

Tisotumab vedotin (HuMax-TF-ADC) is an ADC consisting of three components:

- The human monoclonal antibody (IgG1κ) targeting TF
- A protease-cleavable valine-citrulline linker

- The microtubule disrupting agent MMAE

Literature data from cleavable MMAE-based ADCs include, but are not limited to, CD30-ADC (Younes et al., 2010; Adcetris® Prescribing Information, 2014), CR011-ADC (Hwu et al., 2008), ASG-5ME-ADC (Morris et al., 2012; Coveler et al., 2012), PSMA-ADC (Mega et al., 2012), CD22-ADC (Advani et al., 2012) and CD79b-ADC (Palanca-Wessels et al., 2012). Major toxicities commonly seen with MMAE-based ADCs include peripheral blood neutropenia and late peripheral neuropathies. In general, no major toxicities have been observed below 1 mg/kg when MMAE-based ADCs were administered at a three-weekly regimen.

Data from CD30- ADC dose-escalation trial in Hodgkin's Lymphoma showed no appearance of dose limiting toxicities (DLTs) up to and including 1.5 mg/kg. Furthermore, no grade 3 skin reactions were reported (Younes et al., 2010). In the package insert, skin rash is reported in 27%-31% of patients, none of which were grade 3 or above. An MTD of 1.8 mg/kg was found and the main safety findings of CD30-ADC included peripheral neuropathy, myelosuppression and infusion-related reactions (IRRs). Myelosuppression was also observed during the pre-clinical toxicity studies with dose-related hematological toxicity especially neutropenia and hypocellularity of the bone marrow.

The most common adverse reactions (≥ 20%) reported during treatment with CD30-ADC (brentuximab vedotin [Adcetris® Prescribing Information, 2014]) regardless of causality, were neutropenia, thrombocytopenia, peripheral sensory neuropathy, fatigue, pyrexia, upper respiratory tract infection, nausea, diarrhea, abdominal pain, vomiting, rash and cough. Two cases of anaphylaxis were reported during infusion of CD30-ADC in phase I trials. There were no grade 3 or 4 IRRs reported in the phase II trials. However, grade 1 or 2 IRRs were reported for 19 patients (12%). Serious adverse events (SAEs) regardless of causality were reported in 31% of patients receiving Adcetris. The most common SAEs in patients with Hodgkin's lymphoma were neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumothorax (2%), pyelonephritis (2%) and pyrexia (2%).

In the CR011-ADC trial targeting the protein known as GPNMB, at doses ≤ 0.96 mg/kg, only grade 1 and 2 adverse events (AEs) were recorded, including fatigue, diarrhea, nausea and grade 1 neuropathy and skin rash. At higher doses, grade 3 AEs including, peripheral neuropathy and skin disorders and grade 4 neutropenia were observed. Using a three-weekly approach, grade 3 skin rash was described in the 1.88 mg/kg dose cohort. Dose limiting toxicities were described at 2.63 mg/kg including exfoliative rash in one patient and erythematous, blistering rash in another patient. The latter patient was dose reduced and continued in the trial. At MTD (1.88 mg/kg q3wk), skin rashes are described in 70% of patients with 26% being grade ≥ 3 (Hamid et al., 2010). When more dose intense dose-schedules were introduced (dosing weekly, two of three weeks) a grade 5 toxic epidermal necrolysis (TEN) was observed. Using a weekly dosing regimen, a grade 5 acute renal failure and grade 4 skin rash were observed.

In the ASG-5ME-ADC trials, DLTs were reported as grade 3 troponin elevation and maculo-papular rash when dosed as 3 mg/kg q3wk. Other grade 3 events included fatigue, peripheral neuropathy, anorexia, dyspnea and nausea. When a more dose intense regimen was used, grade 3-4 vomiting and abdominal pain were reported.

In the PSMA-ADC trial, DLTs were described as primarily neutropenia and MTD was determined at 2.5 mg/kg.

During clinical phase II development, two fatal cases of sepsis were observed and dosing was reduced to 2.3 mg/kg going forward. In the CD22-ADC and CD79b-ADC trials, grade 3 AEs occurring in ≥ 10% of patients included neutropenia (CD22) and neutropenia, and leukopenia (CD79b). Both studies reported a recommended phase II dose (RP2D) at 2.4 mg/kg. Grade 3 or 4 AEs observed in more than one patient at RP2D included neutropenia (CD22), neutropenia, anemia, leukopenia and fatigue (CD79b).

The mechanism of action of the antibody-based TF antagonist ALT-836 is binding to TF or the TF-FVIIa complex thereby preventing the association and activation of FX and inhibiting thrombin generation. HuMax-TF inhibits FVIIa binding to human TF and inhibits TF:FVIIa signaling; however HuMax-TF did not inhibit FXa generation.

The main safety issues during treatment with the antibody-based TF antagonist ALT-836 were hematuria and worsening of hematuria of grade 1 and 2. On average the hematuria started 6.7 hours after initiation of treatment and resolved within 29.1 hours without need of medical intervention. No major bleeding or other spontaneous minor bleeding was observed. There were no effects on PT, platelet count, aPTT or plasma levels of D-dimer, prothrombin, fragment 1+2 or fibrinogen at any ALT-836 dose level.

Overall, data on other monoclonal antibodies targeting TF include minor bleeding (hematuria; [ALT-836]). Currently, two other anti-TF monoclonal antibodies are in clinical development within solid tumors (ALT-836 and MORAb-066); no data are available from those studies.

The class effects of the anti-microtubule agents primarily include peripheral neuropathy and myelosuppression.

6.2.3 Clinical Experience

Tisotumab vedotin is being investigated in two clinical trials; GEN701 and GEN702. Each trial consists of two parts; a Dose Escalation part and a Cohort Expansion part. The Dose Escalation part for GEN701 and GEN702 has been finalized. The Cohort Expansion part is ongoing for both trials. As of 16 Aug 2017, 207 patients have been treated with tisotumab vedotin.

GEN701

As of 16 Aug 2017, 147 patients have been dosed with tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg once q3w in the GEN701 Cohort Expansion part.

Summary of Clinical Safety Data from GEN701 Part II (Cohort Expansion part)

Across all indications in the Cohort Expansion part, the most commonly reported AEs observed in at least 29 patients (> 20%) were epistaxis (64%), fatigue (53%), nausea (47%), alopecia (42%), conjunctivitis (42%), constipation (33%), decreased appetite (32%), diarrhea (27%), vomiting (26%) and peripheral neuropathy (26%).

Grade ≥ 3 AEs were reported in 55% of patients. The most frequently reported grade ≥ 3 AEs were fatigue (8%), anemia (6%), abdominal pain (4%), vomiting (4%), hypokalemia (4%), hyponatremia (3%) and conjunctivitis (3%). All other grade ≥ 3 AEs were reported in one or two patients only.

Serious adverse events were reported in 45% of patients. Vomiting was the most frequently reported SAE (4%), followed by abdominal pain (3%), hypokalemia, hyponatremia, general physical health deterioration and anemia (2% each). All other SAEs were reported in one patient (1%) only.

Adverse events leading to discontinuation were reported in 44 patients (30%); across all indications the most frequently AEs leading to discontinuation were peripheral neuropathy (5%), conjunctivitis (4%), peripheral sensory neuropathy (3%) and polyneuropathy (2%). All other AEs leading to discontinuation were reported in one patient (1%) each.

One patient experienced a grade 5 AE possibly related to the IMP (pneumonia preceded by neutropenic sepsis observed in a patient with relapsed prostate cancer).

Two patients experienced an SAE (grade 2 and 3, respectively) of ischemic cerebral stroke, and one patient experienced an incidental finding of a pulmonary embolism possibly related to the IMP. Cancer patients have a well-known increased risk of both arterial and venous thromboembolic events (none of these patients had received anti-coagulant therapy prior to the event), and the observed rates are below the expected rates of thromboembolic events in this patient population (Lyman, 2011; Navi et al., 2017).

The above data indicate a manageable toxicity profile, overall in line with what is expected for an MMAE-based ADC, with the exception of conjunctivitis. An ocular mitigation plan was implemented by Amendment 12 (dated 22 Dec 2016) and has reduced the frequency and severity of ocular adverse events including conjunctivitis in GEN701.

For further details of AEs observed in GEN701 please refer to the Investigator's Brochure.

Summary of Efficacy and Concentration Data from GEN701 Part I and II

Preliminary efficacy results consist of four patients achieving response at some point, of which only one was subsequently confirmed. Of the three unconfirmed responses, two were observed after the patients had already been withdrawn due to AEs, and one had disease progression about four weeks after the response was first observed.

From the Dose Escalation part of GEN701, the maximum observed maximum concentration (C_{max}) for TF-ADC was 62700 ng/mL while the maximum area-under-the-concentration-time curve (AUC_{0-t}) was 2706325.5 hr*ng/mL. For MMAE, the maximum C_{max} was 12100 pg/mL while the maximum AUC_{0-t} was 2776657.4 hr*pg/mL.

GEN702

In the Cohort Expansion part of GEN702 a more frequent dosing regimen of tisotumab vedotin has been tested. As of 16 Aug 2017, 24 patients have been enrolled in the Cohort Expansion part. Patients were initially treated with tisotumab vedotin (HuMax TF ADC) 1.2 mg/kg administered three times every four weeks (3q4w). However, the more frequent

dosing regimen was later discontinued due to severe ocular toxicity despite adherence to the ocular mitigation plan (implemented by Amendment 12 dated 22 Dec 2016), and patients enrolled have instead been offered tisotumab vedotin (HuMax TF ADC) 2.0 mg/kg once q3w, which in GEN701 has been found to be potentially efficacious and safe. The ocular mitigation plan has further been updated (implemented by urgent safety measure dated 23 Jun 2017) in order to specify how to mitigate ocular AEs according to grading and to ensure treatment according to ophthalmologist's guidelines.

Summary of Clinical Safety Data from GEN702 Part II (Cohort Expansion Part)

For further details of AEs observed in GEN702 please refer to the Investigator's Brochure.

Summary of Efficacy and Concentration Data from GEN702 Part I and II

Data are too preliminary to be presented.

6.2.4 Summary of Known and Potential Risks to Human Subjects

The below section is based on data available as of 16 Aug 2017:

Tissue cross-reactivity:

- In both human and cynomolgus monkey tissue, staining was generally observed both on the membrane and in the cytosol. The staining was generally consistent with reported sites of TF expression, indicating expression in various epithelia; mesothelium, endothelium, stromal cells, glial and neuronal cells, peripheral nerves and ganglia, retina, adipose tissue, mononuclear cells (including alveolar macrophages), cardiomyocytes, smooth muscle, glomerular tuft cells, and islet cells. No literature was available describing the observed expression of TF in skeletal muscle, ovarian luteal and thecal cells, testicular spermatogenic and Leydig cells. The staining of these tissue elements may represent an unreported site of TF expression.
- The staining pattern was generally similar between the human and cynomolgus monkey tissue panels examined, with a few exceptions. HuMax-TF and tisotumab vedotin (HuMax-TF-ADC) stained mesothelium in several tissues, endothelium in the spleen, and thecal cells in the ovary in the cynomolgus monkey, whereas staining in these cells and tissues was not observed in human tissues. HuMax-TF and tisotumab vedotin (HuMax-TF-ADC) likewise stained elements in human tissues that were not evident in cynomolgus monkey tissues, and included arachnoid cap cells in cerebellum and spinal cord, ganglion cells in adrenal, striated skeletal myocytes in the eye, intrinsic smooth myocytes in esophagus, stomach, and prostate, islet cells in pancreas, luteal cells in ovary, and spermatogenic cells in testis. These differences are likely to be due to other variations e.g., section, donor, donor age than species differences; however, toxicity to these organs cannot be excluded.

MMAE metabolism:

- MMAE is mainly metabolized by cytochrome CYP3A4 and is capable of inhibiting human CYP3A4/5 at clinically relevant concentrations. Additionally, MMAE is a substrate for the cellular trans-membrane transporter P-glycoprotein (P-gp).

Consequently, as a precaution, patients should not be co-medicated with drugs known to be strong inhibitors of CYP3A4 and/or P-gp.

Specific adverse events:

- Infusion-related reactions have been observed with other MMAE-ADCs. One IRR, including skin rash and swelling of eyes and lips, was observed during non-clinical studies in a female monkey following a second dose of tisotumab vedotin (HuMax-TF-ADC) 3 mg/kg. No IRRs were observed in this animal following the third or fourth dose administration of IMP. Infusion-related reactions have been observed in patients treated with tisotumab vedotin (HuMax-TF-ADC), but the majority of reactions have been mild to moderate. Please refer to the Investigator's Brochure for more information.
- Due to mode of action of tisotumab vedotin (HuMax-TF-ADC) its potential impact on TF-dependent coagulation was investigated *in vitro* in a series of coagulation assays including an FXa generation assay, the standard PT assay, a clotting assay, TEG and a thrombin generation assay. Overall, only relatively minor impact of HuMax-TF on TF-mediated coagulation was observed. No bleeding events were observed in cynomolgus monkeys and PT and aPTT coagulation parameters were unaffected by treatment with tisotumab vedotin (HuMax-TF-ADC) in all repeat-dose toxicology studies. In line with pre-clinical findings, no major impact on aPTT or PT has until now been found in humans treated with tisotumab vedotin (HuMax-TF-ADC) and despite high frequency of mild grade 1 epistaxis (possibly caused by inflammation), no clinically relevant increased bleeding risk have been observed. Please refer to Investigator's Brochure for more detailed information.
- Bone marrow suppression is a common adverse reaction for MMAE-ADCs and was observed in cynomolgus monkeys in relation to treatment with tisotumab vedotin (HuMax-TF-ADC). The observed bone marrow suppression was reversible and mostly reduced total peripheral white cells, notably the neutrophils. In line with these findings, adverse reactions of anemia and neutropenia are frequently reported in patients treated with tisotumab vedotin (HuMax-TF-ADC). Please refer to the Investigator's Brochure for more detailed information and an overview of expected adverse events (RSI table).
- Severe skin toxicity was observed in cynomolgus monkeys following treatment with tisotumab vedotin (HuMax-TF-ADC). The toxicity was dose-related and reversible and characterized by skin reddening and dry flaky skin. In a few animals the skin changes deteriorated, possibly in connection with accidental skin wounds that became secondarily infected, and three animals had to be terminated for animal welfare reasons. Mild events of rash, maculopapular rash and other skin reactions like pruritus have frequently been reported in patients treated with tisotumab vedotin (HuMax-TF-ADC), but only one serious event of rash (grade 4) has been reported across all trials. Please refer to the Investigator's Brochure for more information.
- Peripheral neuropathy is a well-known AE of treatment with chemotherapeutic drugs including other MMAE-based ADCs. Peripheral neuropathy (including the preferred terms: neuropathy peripheral, peripheral sensory neuropathy, peripheral motor

neuropathy and polyneuropathy) has been observed in patients treated with tisotumab vedotin (HuMax-TF-ADC), however only few patients experienced a grade ≥ 3 event. This is in line with what is expected for an MMAE-ADC and also reflecting that most subjects in GEN701 were heavily pre-treated prior to entering this trial. Please refer to the Investigator's Brochure for more information.

- Severe events of hepatotoxicity have been observed in relation to treatment with other MMAE-based ADCs but pre-clinical studies in cynomolgus monkeys found no hepatotoxicity of tisotumab vedotin (HuMax-TF-ADC). Increased liver enzymes have been reported in patients treated with tisotumab vedotin, however the majority of the events have been grade 1 and 2. Please refer to the Investigator's Brochure for more information.
- Testicular toxicity was observed in cynomolgus monkeys administered 1, 3 and 5 mg/kg of tisotumab vedotin (HuMax-TF-ADC). Full recovery was observed at 1 mg/kg but only partial reversibility was observed after 6 weeks recovery at 3 and 5 mg/kg tisotumab vedotin (HuMax TF-ADC). Tisotumab vedotin (HuMax-TF-ADC) may have an adverse effect on spermatogenesis in man.

Please refer to Section 6.2.3 for a summary of the safety data obtained in GEN701 part II.

6.3 Clinical Study Rationale

6.3.1 Patient Population

Tissue factor is aberrantly expressed in many solid tumors as well as in the tumor vasculature. To retain possible benefit for patients, the patient population will be restricted to indications where TF is known to be expressed and where the usage of systemic tubulin-inhibition is a part of SoC in the clinic.

The patient population in the Dose Escalation part will encompass patients with advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophagus or lung (NSCLC) who have failed available standard treatments or who are not candidates for standard therapy.

Based on the safety data of the Dose Escalation part and the DMC and sponsor's Safety committee recommendation, the Cohort Expansion part will encompass patients with advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophagus, lung (NSCLC) or SCCHN who have failed available standard treatments as specified in the inclusion criteria. Patients included in the "bladder cancer" cohort will encompass patients with urothelial carcinomas (transitional cell carcinomas) regardless of the initial site of origin of the tumor (renal pelvis, ureter or bladder lumen).

6.3.2 Study Design

This is a phase I/II, open-label, dose-escalation, safety study of tisotumab vedotin HuMax-TF-ADC) dosed once q3wk in a mixed patient population with solid tumors to establish the safety profile. The study consists of two parts: A Dose Escalation part followed

by a Cohort Expansion part. The Dose Escalation part is considered FIH and the Cohort Expansion part a phase II.

The Dose Escalation part will have a standard 3 (+3) design. In each dose cohort, the initial three patients must include at least two different cancer types. With eight planned dose levels, it is anticipated to include a maximum of 48 patients.

The Cohort Expansion part will enroll approximately 169 patients who will be treated with a regimen based on the data obtained from the Dose Escalation part. The Cohort Expansion part will provide further safety, tolerability, PK and anti-tumor activity data from patients with cancer types that express TF.

6.3.3 Dose Rationale

Based on toxicology data from the 13-week repeat dose toxicology study in cynomolgus monkeys the highest non-severely toxic dose (HNSTD) was set at 3 mg/kg in females. A safety factor of 10 was then applied to the HNSTD resulting in a starting dose of 0.30 mg/kg.

Data from cleavable MMAE-based ADC described in literature, including CD30-ADC, CR011-ADC, ASG-5ME-ADC, PSMA-ADC, CD22-ADC and CD79b-ADC, have indicated that no significant safety signals are observed at doses below or at 1 mg/kg given q3wk and MTD and/or RP2D are within the range of 1.8 mg/kg to 2.5 mg/kg across the molecules when q3wk dose regiments were used. Based on these literature findings and preclinical data of tisotumab vedotin (HuMax-TF-ADC) no major toxicity of tisotumab vedotin is anticipated in the clinic at doses below 1 mg/kg. The Dose Escalation part of the study includes eight dose cohorts; 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.2 and 2.6 mg/kg, corresponding to the following dose increments: 100%, 50%, 33%, 25%, 20%, 22% and 18%. The maximum tested dose will be 2.6 mg/kg.

Tisotumab vedotin (HuMax-TF-ADC) will be administered once q3wk. This dosing frequency is based on toxicokinetics and toxicology data obtained in cynomolgus monkeys, suggesting adequate recovery of neutrophils, red cell parameters and skin changes over a three-week period and otherwise an acceptable safety profile. No accumulation of tisotumab vedotin (HuMax-TF-ADC) is anticipated based on the proposed dose interval. Main study period will encompass four treatment cycles and allow patients with potential benefit (defined as stable disease [SD] or better) to continue for up to eight additional treatment cycles (for a maximum of twelve cycles in total). At the end of this period, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or progressive disease (PD) is observed. If a specific safety signal is observed in one of the tested indications in the Dose Escalation part, the sponsor will retain the possibility to include more patients at the same dose level. Finally, the sponsor in collaboration with the DMC has the possibility to add intermediate dose cohorts to better define MTD.

In each dose cohort in the Dose Escalation part, a minimum of ten days between administration of first dose in patient 1 and patient 2 and minimum of one day between the subsequent patients will be implemented.

The Cohort Expansion Part will recruit patients to each of the indication arms in parallel, without any delay between administrations.

6.4 Immunogenicity Assay Strategy for tisotumab vedotin (HuMax-TF-ADC)

Patient serum samples will be assessed for the presence of anti-drug antibodies (ADA) against tisotumab vedotin (HuMax-TF-ADC) in a screening assay.

Positive samples will be assessed in a confirmatory assay where samples will be pre-incubated with HuMax-TF-ADC. Confirmed positive samples will subsequently be titrated to establish an ADA titer.

To determine the specificity of ADA response of confirmed positive samples, it will be assessed whether the response is directed against the toxin or the antibody moiety of the drug (binding region assay) and a neutralization assay will be performed.

The binding region assay will use the format of the confirmatory assay and samples will be pre-incubated with HuMax-TF-ADC, HuMax-TF or free MMAE.

For the neutralization assay, several potentially suitable assay formats are under evaluation. Two assays are based on the mechanism of action of HuMax-TF-ADC; a cell-based internalization assay of HuMax-TF-ADC and a cell-based killing assay for HuMax-TF-ADC. Alternatively, a competitive ligand binding assay; either cell-based or immobilized recombinant ligand-based will be considered.

During study conduct, AEs and laboratory data will be collected to monitor all patients closely for potential safety signals. In addition, potential biologic activity determined by applied CT scanning, CA 125 and PSA measurements will be assessed. The association between positive/non-positive ADA and PK (pre-dose, C_{max}), major safety signals (CTCAE grade ≥ 3) and efficacy information (change in tumor size by CT-scan) will be explored.

6.5 Rationale for Exploratory Endpoints

6.5.1 Tumor Biopsy

In this clinical study, tumor tissue samples will be collected at screening and TF expression will be determined by IHC using a TF-specific antibody. In the Dose Escalation part an archived sample may be used as screening sample. The most recent available archived sample should be used. In addition to TF-expression analysis, morphological analysis of the tumor section will be done using standard histological methods (i.e., hematoxylin-eosin staining). The results will be used to explore the clinical utility of such an IHC assay for the characterization of TF expression in tumors and to get a first impression on a possible correlation between tumor TF expression and clinical safety and/or biological activity of tisotumab vedotin (HuMax-TF-ADC).

In the Cohort Expansion part of the study, tumor biopsies are collected at screening from each patient. The most recent available archived sample can be used. If no biopsies are available, a new biopsy must be obtained before dosing. In addition, an optional tumor biopsy may be obtained three weeks after last dosing (+ 2 weeks). TF expression levels, as determined using the IHC assay, will be compared between the two biopsies to evaluate

potential modulation of TF expression due to tisotumab vedotin (HuMax-TF-ADC) treatment.

6.5.2 Biomarkers

Plasma samples are collected for retrospective analysis in a centralized laboratory of i) circulating TF, ii) an array of 1129 different proteins, and iii) total levels of circulating cell-free deoxyribonucleic acid (cfDNA).

6.5.2.1 Circulating Tissue Factor in Plasma

Enhanced levels of circulating TF have been reported in the plasma of patients with many different types of cancer, including cancers evaluated in GEN701 (Strijbos et al., 2010, Golding-Lang et al., 2008, Han et al., 2006). Circulating TF may exist as full length TF associated with (tumor) cell-derived microvesicles, as the soluble alternative splice variant of TF (alternatively spliced TF), or as truncated TF. Levels of circulating TF may correlate with the tumor mass of TF expressing tumors. Accordingly, circulating TF may provide an easy accessible and sensitive pharmacodynamic marker to monitor patient responses to tisotumab vedotin (HuMax-TF-ADC).

6.5.2.2 Protein Biomarkers

Although the GEN701 study is primarily setup to evaluate safety and dosing of tisotumab vedotin (HuMax-TF-ADC), plasma samples are collected to identify potential markers for efficacy of HuMax-TF-ADC. In these samples an array of 1129 proteins is measured using the SOMAscan technology™ [redacted], US) and/or another existing platform for protein analyses.

6.5.2.3 Circulating Free DNA

Cell-free DNA fragments are commonly observed in plasma of healthy individuals, and are thought to originate from dying or apoptotic cells as part of normal tissue turnover. In patients with advanced cancer, including NSCLC, ovarian cancer and bladder cancer, enhanced levels of cfDNA have been reported (Gautschi, 2004; Ellinger et al, 2008, Choudhuri et al., 2014; Spindler et al., 2012). Although the factors that influence changes in total cfDNA levels in cancer patients are not fully understood, a substantial portion of circulating cfDNA in cancer patients is thought to originate from tumor cells. Importantly, a decrease in cfDNA levels was found to be an indicator of response to treatment in ovarian cancer, NSCLC and breast cancer (Gautschi, 2004; Choudhuri et al., 2014; Dawson et al., 2013). Treatment with tisotumab vedotin (HuMax-TF-ADC), if effective, may result in a reduction of cfDNA levels. With the purpose of monitoring changes in levels of cfDNA during treatment with HuMax-TF-ADC, blood plasma samples will be taken and cfDNA will be isolated.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

7.1.1 Primary Study Objective

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

7.1.2 Secondary Study Objectives

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

7.2 Study Endpoints

7.2.1 Primary Endpoint

The primary endpoint is the evaluation of AEs: incidences of AEs, SAEs, infusion-related AEs, CTCAE grade ≥ 3 AEs, and AEs related to study drug during the study.

7.2.2 Secondary Endpoints

- Safety laboratory parameters (hematology, biochemistry, coagulation factors and flow cytometry).
- Skin disorders.
- Bleeding events.
- Neuropathy.
- PK parameters (clearance, volume of distribution and $AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$, C_{max}, time of C_{max} [T_{max}], pre-dose values, and half-life of tisotumab vedotin (HuMax-TF-ADC) and free toxin [MMAE]).
- Immunogenicity (ADA) of tisotumab vedotin (HuMax-TF-ADC).
- Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations), change in PSA and CA 125.
- Objective Response (Complete Response [CR] or Partial Response [PR]), Disease Control (CR, PR or SD) after 6, 12, 24 and 36 weeks, Progression-Free Survival (PFS) and Duration of Response (DoR).

7.2.3 Exploratory Endpoints

- TF expression in tumor biopsies.
- Circulating TF.
- Protein biomarker.
- cfDNA.

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a dose-escalating, open-label, multicenter phase I/II safety study of tisotumab vedotin (HuMax-TF-ADC) dosed once q3wk in a mixed population of patients with solid tumors known to express TF and where the use of systemically administered tubulin inhibitors is part of SoC. The study consists of two parts: a Dose Escalation part and Cohort Expansion part. The Dose Escalation part is considered FIH and the Cohort Expansion part a phase II.

8.1.1 Dose Escalation Part

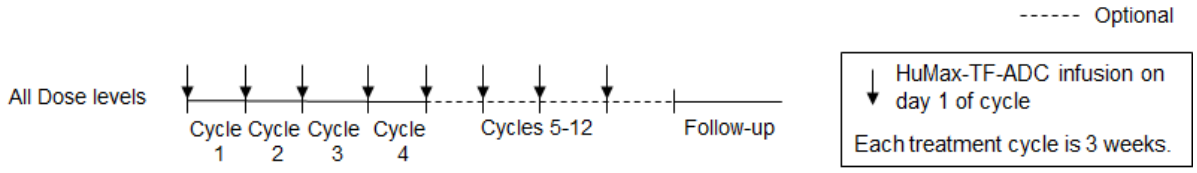
The Dose Escalation part is a standard 3 (+3) design which will evaluate tisotumab vedotin (HuMax-TF-ADC) at doses of 0.30 mg/kg and up (0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.2 and 2.6 mg/kg).

In the absence of unacceptable first cycle toxicities, doses are escalated in the subsequent cohorts, as deemed appropriate by the DMC and confirmed by sponsor. If unacceptable first cycle toxicities are observed, cohorts will be expanded from three to six patients. Depending on the nature of the observed event, the DMC may require that at least one patient of the additional three patients to be included 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. Further details of the dose-escalation steps are provided in Section 8.4.12.

In each dose cohort, the initial three patients included must include at least two different cancer types. Patients will be treated for four cycles or until unacceptable toxicity is observed. Patients showing clinical benefit, defined as SD or better, can receive up to a maximum of eight additional treatment cycles (for a maximum of twelve cycles in total). At the end of this period, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or PD is observed.

See Figure 1 below for illustration.

Figure 1: Dose Escalation Part: Dose Levels and Cohorts - Dosing Period (Cycles 1-4) and Extended Dosing Period (Cycles 5-12)



Twelve cycles are expected to correspond to 36 weeks.

8.1.2 Cohort Expansion Part

The aim of the Cohort Expansion part is to provide further safety, tolerability, PK and anti-tumor activity data from patients with cancer types that express TF. Recruitment will be

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

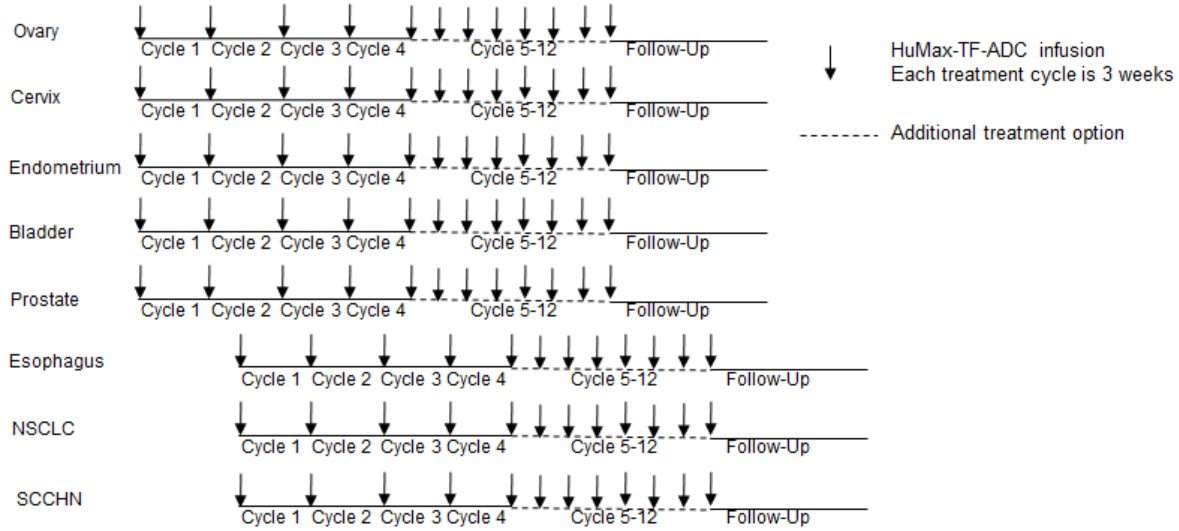
Cervical and endometrial indications will be expanded from 14 to 30 patients if, and only if, a responder is observed (evaluated after last patient has had four cycles) or, in case of no responders, the DMC evaluates whether it is nevertheless meaningful to expand. If one of these two indications does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

Patients will be treated with the dose determined from the Dose Escalation part of the study by the DMC and the sponsor's Safety committee. Reduced dose can be administered in accordance with the mitigation strategies (Section 8.4.4 to 8.4.10) 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.

Patients showing clinical benefit, defined as SD or better, can receive up to a maximum of eight additional treatment cycles (for a maximum of twelve cycles in total). At the end of this period, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or PD is observed.

See Figure 2 below for illustration.

Figure 2: Cohort Expansion Part: Dosing Period (Cycles 1-4) and Extended Dosing Period (Cycles 5-12)



Twelve cycles are expected to correspond to 36 weeks.

8.1.3 Study Overview

A study overview is described below. The study flowchart is in Table 1 for the Dose Escalation part and in Table 2 for the Cohort Expansion part. Study evaluations by visit are detailed in Section 9.

8.1.3.1 Screening Phase (Visit 0)

Subjects will provide written informed consent. Medical history, physical examination, laboratory studies, ophthalmological evaluation and CT imaging will be performed to determine baseline disease status and study eligibility. The medical history, physical examination, potential biopsies, ECG and laboratory studies (including biomarkers) must be performed within 21 days before study entry (Visit C1-V1). CT imaging must be performed within four weeks before study entry (Visit C1-V1).

A patient may be rescreened one time only. A rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

8.1.3.2 Treatment Phase (C1 to CX)

Dose Escalation Part

The investigator must have evaluated the patient's eligibility and confirm receipt of sponsor decision and patient number before the patient's first infusion.

Tisotumab vedotin (HuMax-TF-ADC) will be administered every 21 days. Dose-escalation to MTD is anticipated to involve approximately eight dose levels with an anticipated maximum dose level of 2.6 mg/kg (not including potential intermediate dose cohorts).

Patients will receive four cycles (doses) of tisotumab vedotin (HuMax-TF-ADC) at 21-day intervals. Thus, the treatment period will last for twelve weeks, or until disease progression.

After four cycles, if there is evidence of the patient benefitting from treatment, at the discretion of the treating physician after agreement with Genmab on the patient status, there is an option to continue in the study for up to a maximum of eight additional cycles (24 weeks) or until unacceptable toxicity according to protocol is observed.

The treatment period will have a maximum duration of 36 weeks.

Cohort Expansion Part

The investigator must have evaluated the patient's eligibility and signed the Screening Evaluation Form before the patient's first infusion.

Tisotumab vedotin (HuMax-TF-ADC) will be administered every 21 days. Approximately 169 patients will receive four cycles (doses) of tisotumab vedotin (HuMax-TF-ADC) at the dose determined by the sponsor in agreement with the DMC based on the Dose Escalation part of the study. The treatment period will last for twelve weeks or until disease progression.

After four cycles, if there is evidence of the patient benefitting from treatment, at the discretion of the treating physician, there is an option to continue in the study for up to a maximum of eight additional cycles (24 weeks) or until unacceptable toxicity is observed.

The treatment period will have a maximum duration of 36 weeks.

8.1.3.3 Unscheduled Visit (U1 to UX)

If deemed necessary by the investigator the patient may be called in for an unscheduled visit(s). During an unscheduled visit the investigator can perform any study clinical or laboratory assessment deemed necessary. The visit date and reason for visit must be recorded in the patient's medical records and electronic case report form (eCRF).

For the Cohort Expansion part, an unscheduled visit may also be used to collect information about the tumor biopsy obtained three weeks after last treatment (optional), or to document a repeat CT-scan to confirm response.

8.1.3.4 Follow-up Phase (FU1 to FU4)

If the patient withdraws from treatment and has not started new anti-cancer treatment, or if the patient completes all treatment cycles, the patient will be followed by the site every six weeks for a maximum of four visits (24 weeks) or until PD, other treatment is initiated or the patient withdraws from the study due to other reason, whichever occurs first. After that, the patient will return for an End of Study Visit (EOS).

8.1.3.5 End of Study Visit (EOS)

If a patient completes all the follow-up visits, the EOS Visit should be performed four weeks after Follow-up Visit 4. In case of withdrawal from the study, the EOS Visit will be performed as soon as possible. The EOS Visit will include most assessments performed at the Screening Visit, and response assessments.

8.1.3.6 Safety Follow-up Visit (SFU)

Patients who withdraw from the study before Follow-up Visit 1 will return for a Safety Follow-up Visit 30 days after the last IMP dosing. In the Safety Follow-up Visit, only SAEs

will be assessed, as well as any new anti-cancer treatment, if applicable, in the Cohort Expansion part. If the patient has died within the 30 days, this should be entered as an AE in the eCRF and reported as an SAE.

Table 1: Study Flow Chart – Dose Escalation Part

Treatment Cycle	**Screening**	**Cycle 1-2**						**Cycle 3-4**			**Cycle 5-12[1]**			**Follow Up**	**EOS[2]**	**Withdrawal Safety Follow Up**	**Unsched**
Visit Number	**0**	**1[3]**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**1**	**2**	**3**	**1-4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**2d**	**4d**	**8d**	**11d**	**15d**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**6 weekly**	**-**	**30 days after last dosing[5]**	**-**
Visit window[4]		**±1d**	**-**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**±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[20]	X													X		
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X[16]
ECG[10]	X	X						X			X				X		X[16]
CT-Scan	X[11]							X[12]			X[12]			X	X[12]		X[16]
ECOG Performance Status	X	X						X			X				X		X[16]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[16]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[16]
Study Drug Administration		X						X			X						
Bleeding Assessment	X	X	X	X	X	X	X	X			X				X		
Skin Assessment	X	X	X	X	X	X	X	X			X			X	X		X[16]
Neuropathy Assessment	X	X				X		X		X	X		X	X	X		X[16]

Treatment Cycle	**Screening**	**Cycle 1-2**						**Cycle 3-4**			**Cycle 5-12[1]**			**Follow Up**	**EOS[2]**	**Withdrawal Safety Follow Up**	**Unsched**
Visit Number	**0**	**1[3]**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**1**	**2**	**3**	**1-4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**2d**	**4d**	**8d**	**11d**	**15d**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**6 weekly**	**-**	**30 days after last dosing[5]**	**-**
Visit window[4]		**±1d**	**-**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±7d**	**-**	**+14d**	**-**
Radionuclide Bone Scan[13]	X										X						X[16]
LABORATORY ASSESSMENTS[14]																	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[16]
Biochemistry	X	X			X		X	X	X	X	X	X	X	X	X		X[16]
Coagulation factors	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[16]
PSA[13]	X	X						X			X			X	X		X[16]
CA 125[15]	X	X						X			X			X	X		X[16]
Flow Cytometry		X[19]									X[19]				X		X[16]
Pregnancy Test	X	X													X		X[16]
ADA (Immunogenicity)	X	X						X			X			X			X[16]
Hepatitis B, C, CMV, HPV[17]	X														X		X[16]
PK Sampling[21]	X	X	X		X		X	X			X			X			X[16]
Tumor biopsy	X[18]																X[16]
Biomarkers	X										X[22]						

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=End of Study; HCV=hepatitis C virus; HPV= human papilloma virus; PCR=polymerase chain reaction; PK=pharmacokinetic; PSA=prostate specific antigen

Footnotes to Study Flowchart – Dose Escalation Part

[1] Additional treatment only if patient shows response of SD or better and after approval by Genmab.

[2] If patient is withdrawn from study during treatment or Follow-up period, the EOS Visit should be performed as soon as possible after decision of withdrawal. If patient completes all Follow-up visits, the EOS Visit should be performed four weeks after Follow-up Visit 4.

[3] The patient shall stay hospitalized the first 24 hours after the infusion and be discharged the following day after assessments and 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] For patients who withdraw from the study before Follow-up Visit 1. Only SAEs will be assessed.
[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 C1-V1 should be recorded as medical history (see 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 study, only body weight is measured on dosing days, as part of the dose calculation. If body weight is assessed ≤ 3 days before the day of the planned dosing, this value can be used and is the weight recorded in the eCRF.
[9] 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 24 hours after end of infusion of the 2 first infusions and until 2 hours after the remaining infusions, as indicated in Section 10.5.
[10] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before each infusion of the study drug, in accordance with the ECG Specifications Manual.
[11] Within four weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen, and pelvis performed during screening. 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 study. 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 2nd cycle, i.e., on Day 1 of Cycles 3, 5, 7, 9 and 11, 21 days (± 3 days) after Day 1 of Cycle 12, and at the EOS Visit. 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. To be completed as indicated to confirm response, new symptoms, end of study or physician discretion. If reduction of target lesions ≥ 30% in size is observed, one repeat CT-scan will be performed after four weeks to substantiate response.
[13] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every twelve 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 four weeks prior to Visit C1-V1.
[14] Hematology, biochemistry, serology and pregnancy test will be analyzed locally at the sites. All other laboratory parameters will be analyzed centrally.
[15] For patients with ovarian cancer.
[16] Optional.
[17] 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 EOS, only antibodies to CMV antigen will be assessed.
[18] Archived biopsy 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.
[19] Flow cytometry only on Cycle 1 and Cycle 5.
[20] Including a baseline visual acuity assessment at screening.
[21] See Table 3 for details of PK samplings.
[22] Only on Cycle 5.

Table 2: Study Flow Chart – Cohort Expansion Part

Treatment Cycle	**Screening**	**Cycle 1-2**			**Cycle 3-4**			**Cycle 5-12**[1]			**Follow Up**	**EOS**[2]	**Withdrawal Safety Follow Up**	**Unscheduled**
Visit Number	**0**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1-4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**6 weekly**	**-**	**30 days after last dosing**[4]	**-**
Visit window[3]		**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±7d**	**-**	**+14d**	**-**
Informed Consent	X[5]													
Eligibility Criteria	X													
Demographics	X													
Medical History[6]	X													
Height and Body weight[7]	X	X			X			X				X		
Physical Examination	X	X										X		
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X		X		X[15]
ECG[9]	X	X			X			X				X		X[15]
CT-Scan	X[10]				X[11]			X[11]			X	X[11]		X[15]
ECOG Performance Status	X	X			X			X				X		X[15]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X[15]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X		X[15]
Pre-infusion Medication[23]		X			X			X						
Study Drug Administration		X			X			X						
Bleeding Assessment	X	X		X	X			X				X		
Skin Assessment	X	X		X	X			X			X	X		X[15]
Neuropathy Assessment	X	X		X	X			X			X	X		X[15]
Ophthalmological Evaluation	X		X[20]			X[20]			X[20]			X[20]		X[20]
Radionuclide Bone Scan[12]	X							X			X			X[15]
New Anti-cancer Treatment												X	X	X[15]
LABORATORY ASSESSMENTS[13]														
Hematology	X	X	X	X	X	X	X	X	X	X	X	X		X[15]

Treatment Cycle	**Screening**	**Cycle 1-2**			**Cycle 3-4**			**Cycle 5-12**[1]			**Follow Up**	**EOS**[2]	**Withdrawal Safety Follow Up**	**Unscheduled**
Visit Number	**0**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1-4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**6 weekly**	**-**	**30 days after last dosing**[4]	**-**
Visit window[3]		**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±7d**	**-**	**+14d**	**-**
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X		X[15]
Coagulation factors	X	X	X	X	X			X			X	X		X[15]
PSA[12]	X	X			X			X			X	X		X[15]
CA 125[14]	X[14]	X			X			X			X	X		X[15]
Flow Cytometry		X[16]						X[16]				X		X[15]
Pregnancy test[17]	X	X			X			X			X	X		X[15]
ADA (Immunogenicity)	X	X			X			X			X			X[15]
Hepatitis B, C, CMV, HPV[18]	X											X		X[15]
PK Sampling[19]	X	X	X	X	X			X			X			X[15]
Tumor Biopsy	X[21]											X[21]		X[15]
Biomarkers	X						X[22]							

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=End of Study; HCV=hepatitis C virus; HPV= human papilloma virus; PCR=polymerase chain reaction; PK=pharmacokinetic; PSA=prostate specific antigen

Footnotes to Study Flowchart – Cohort Expansion Part
[1] Additional treatment only if patient shows response of SD or better.
[2] If patient is withdrawn from study during treatment or Follow-up period, the EOS Visit should be performed as soon as possible after decision of withdrawal. If patient completes all Follow-up visits, the EOS Visit should be performed four weeks after Follow-up Visit 4.
[3] 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.
[4] For patients who withdraw from the study before Follow-up Visit 1. Only SAEs will be assessed.
[5] Informed consent can be obtained outside the Screening Visit window, i.e. may be reasonably prior to the screening date.
[6] Signs and symptoms occurring between Visit 0 and Visit C1-V1 should be recorded as medical history (see Section 10 for details).
[7] Height is only assessed at the Screening Visit. During the study, only body weight is measured on dosing days, as part of the dose calculation. If body weight is assessed ≤ 7 days before the day of the planned dosing, this value can be used and is the weight recorded in the eCRF.

[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 infusion, as indicated in Section 10.5.
[9] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before each infusion of the study drug, in accordance with the ECG Specifications Manual.
[10] Within four weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen, and pelvis performed during screening. 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 study. In patients with SCCHN additional CT-scan of neck will be performed during screening. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.
[11] At the end of every 2nd cycle, i.e., on Day 1 of Cycles 3, 5, 7, 9 and 11, 21 days (± 3 days) after Day 1 of Cycle 12, and at the EOS Visit. 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. To be completed as indicated to confirm response, new symptoms, end of study or physician discretion. If reduction of target lesions ≥ 30% in size is observed, one repeat CT-scan will be performed after four weeks to substantiate response.
[12] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every twelve weeks, 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 four weeks prior to Visit C1-V1.
[13] All laboratory parameters will be analyzed centrally.
[14] For patients with ovarian and endometrial cancer. In patients with ovarian cancer, the screening sample should be taken within two weeks before starting the treatment.
[15] Optional.
[16] Flow cytometry only on Cycle 1 and Cycle 5.
[17] At the screening visit; every second cycle, i.e., on Day 1 of Cycles 1, 3, 5, 7, 9, 11; at the Follow Up visits and at the EOS visit.
[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 SCCHN and cervical cancer. At EOS, only antibodies to CMV antigen will be assessed.
[19] See Table 4 for details of PK samplings.
[20] At screening and at every second cycle, i.e., Day 8 of Cycles 2. 4. 6. , 8, 10 and 12. Patients experiencing ocular symptoms must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).
[21] The most recent available archived sample can be used. If no biopsies are available, a new biopsy must be obtained before dosing. In addition, an optional sample may be obtained 3 weeks (+ 2 weeks) after last dosing; this should be entered as an unscheduled visit (Section 10.18).
[22] Only on Cycle 4.
[23] Preventive eye therapy to be administered in relation to infusions as detailed in Section 8.4.8.

Table 3: PK Sampling in the Dose Escalation Part

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

[1] *Time window for the Day 2 sampling in the Dose Escalation Part is 24 hours ± 2 hours after end of infusion on Day 1.*
[2] *Allowed time windows are indicated in parentheses.*
[3] *Optional.*

Table 4: PK Sampling in the Cohort Expansion Part

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

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

8.2 Study Duration and End of Study

Enrolment period in the Dose Escalation part is planned to last approximately 21 months. Enrolment period in the Cohort Expansion part is planned to last approximately 30 months.

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

The end of study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last patient in the study or the date the study is closed by the sponsor, whichever occurs first.

All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion, as directed by the site monitor. The IEC/IRB will be notified when the study has been completed.

Genmab A/S reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrolment with respect to quality or quantity.

If the study is prematurely terminated or suspended, Genmab A/S (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IEC/IRB should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused study drug and other materials or supplies provided by the sponsor.

8.2.1 Study Stopping Criteria

If any of the following occur, administration of the study drug will be stopped and no additional patients will be included into the study:

1) Grade ≥ 3 anaphylactic reaction to tisotumab vedotin (HuMax-TF-ADC) in any patient.
2) Other events that, in the judgment of the sponsor Medical Officer, are deemed serious enough to warrant immediate review by the DMC.
3) Any other safety finding assessed as related to tisotumab vedotin (HuMax-TF-ADC) that, in the opinion of the sponsor, contraindicates further dosing of study patients.

If any of the above-listed events occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted by the DMC to determine whether dosing and study entry should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the sponsor's Safety committee is required for resumption of the study in the event that the study is interrupted because of one of the above-listed events. Where applicable, regulatory authorities IECs/IRBs will be notified of any actions taken with the study.

Any patients who have already received the study drug and are currently in the study at the time study stopping criteria are met will continue to be followed by the investigator for safety.

Withdrawal criteria for individual patients are provided in Section 8.3.4.

8.3 Study Population

The Dose Escalation part is planned to be performed in a maximum of five sites in Denmark, United Kingdom and the US, with up to 30 additional sites to be included in Europe and the US for the Cohort Expansion part. Approximately 310 patients will be screened to ensure that up to 217 patients (anticipated screen failure rate of 30%) are enrolled in the study.

A maximum of 48 patients are planned to be enrolled in the Dose Escalation part: up to six patients per dose level for eight dose levels. Approximately 169 patients will be enrolled in the Cohort Expansion part.

The patient population in the Dose Escalation part will encompass patients with advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophagus or NSCLC who have failed available standard treatments or who are not candidates for standard therapy.

The patient population in the Cohort Expansion part will encompass patients with unmet medical need as specified under Inclusion Criterion 1 (Section 8.3.1).

8.3.1 Inclusion Criteria

Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.

Patients **MUST** satisfy all of the following entry criteria before they will be allowed to participate in the study:

1. For the Dose Escalation part: Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, or NSCLC who have failed available standard treatments or who are not candidates for standard therapy.

   For the Cohort Expansion part: Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, head and neck (SCCHN), esophagus, or lung (NSCLC) who have failed the following anti-cancer therapy:

   - Bladder cancer (including urothelial carcinomas [transitional cell carcinomas] regardless of the initial site of origin of the tumor: renal pelvis, ureter or bladder lumen): failing platinum-based therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
   - CRPC: failing docetaxel and either abiraterone OR enzalutamide. Patients must have received no more than two prior chemotherapy-based regimens and a maximum of six prior treatment regimens for advanced disease.

- Ovarian cancer: resistant to at least one platinum-based therapy and after failing at least one line of taxane-containing therapy (isolated CA 125 progression does NOT qualify for study entry). Patients with primary platinum refractory disease are excluded. Patients must have received no more than five prior treatment regimens for advanced disease.
- Cervical cancer: failing a platinum-based regimen. Patients must have received no more than four prior treatment regimens for advanced disease.
- Endometrial cancer: failing platinum-based therapy. Patients must have received no more than four prior treatment regimens for advanced disease (excluding adjuvant chemotherapy).
- Esophageal cancer (esophageal cancer or gastro-esophageal junction [GEJ] cancer): failing platinum-based therapy with or without taxanes depending on established SoC therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
- NSCLC: failing at least one platinum-based regimen. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations should have been treated with appropriate targeted therapy before study entry. Patients must have received no more than four (five allowed for patients with EGFR mutated adenocarcinomas) prior treatment regimens for advanced disease.
- SCCHN: refractory to platinum-based therapy, also failing an anti-EGFR-based therapy if patient is eligible and if anti-EGFR therapy is part of the established SoC therapy. Patients must have received no more than one prior platinum-based and in total three prior treatment regimens for advanced disease.

2. Patients must have measurable disease according to RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 (Eisenhauer et al, 2009).
   - A minimum of one lesion ≥ 10 mm in the longest diameter (LD) from a non-irradiated area. If target lesion(s) are located within previously irradiated area only, the patient can be enrolled only if there has been demonstrated progression in the "in field" lesion and after sponsor acceptance.
     a. Lymph nodes lesion ≥ 15 mm in the shortest diameter from a non-irradiated area.
   - Patients with prostate cancer must be clinically refractory and resistant to hormone therapy as documented by progression (CRPC) and can be included based on prostate specific antigen (PSA) and/or bone metastases according to the Prostate Cancer Working Group Guideline (Scher et al., 2008).
   - Patients with ovarian cancer can be included based on CA 125 positivity according to the Gynecologic Cancer Intergroup Guideline (Rustin et al., 2004) in the Dose Escalation part only.
3. Age ≥ 18 years.

4. Acceptable renal function defined as:
    - Glomerular filtration rate (Cockcroft-Gault) > 45 mL/min.
5. Acceptable liver function defined as:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN); if liver tumor/ metastases are present, then ≤ 5 × ULN is allowed.
    - Bilirubin ≤ 1.5 × ULN, except in patients diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN.
6. Acceptable hematological status (hematologic support is allowed if administered at least one week before Cycle 1 Day 1) defined as:
    - Hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL).
    - Absolute neutrophil count (ANC) ≥ 1500/µL (1.5×10^9/L).
    - Platelet count ≥ 100×10^9/L.
7. Acceptable coagulation status defined as:
    - INR ≤ 1.2 (without anticoagulant therapy).
    - aPTT ≤ 1.25ULN.
    - patients on stable doses of therapeutic anti-coagulative treatment for ≥ 8 weeks (e.g., warfarin) must have an INR ≤ 3.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Life expectancy of at least three months.
10. A negative serum pregnancy test (if female and aged between 18-55 years old).
    - Women who are pregnant or breast feeding are not to be included.
11. Patients, both females and males, of reproductive potential must agree to use adequate contraception during and for six months after the last infusion of tisotumab vedotin (HuMax-TF-ADC).
    - Adequate contraception for women is defined as hormonal birth control or an intrauterine device (see Section 10.16.6). In countries where two highly effective methods of contraception are required this will be an inclusion criterion (refer to Appendix 2).
    - Male patients must be willing to use a latex condom during any sexual contact with females of childbearing potential during and for six months after the last infusion of tisotumab vedotin (HuMax-TF-ADC), even after having undergone a successful vasectomy. It is recommended that fertile males consider having semen specimen obtained for storage for potential future conception.
12. Following receipt of verbal and written information about the study, patients must provide signed informed consent before any study-related activity is carried out.

8.3.2 Exclusion Criteria

If any of the following apply, the patient **MUST NOT** enter the study:

Hematological

1. Known past or current coagulation defects leading to an increased risk of bleeding.
2. Diffuse alveolar hemorrhage from vasculitis.
3. Known bleeding diathesis.
4. Ongoing major bleeding, defined as:
    - Symptomatic bleeding in critical area organ, such as intracranial, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or
    - Bleeding causing a drop in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or bleeding leading to transfusion of two or more units of whole blood or red cells.
5. Trauma with increased risk of life-threatening bleeding or history of severe head trauma or intracranial surgery within two months of study entry.

Cardiovascular

6. Have clinically significant cardiac disease, including:
    - Unstable angina.
    - Acute myocardial infarction within six months of the Screening Visit.
    - Known congestive heart failure (Grade III or IV as classified by the New York Heart Association); and/or a known decreased cardiac ejection fraction of < 45%.
7. A baseline QT interval as corrected by Fridericia's formula (QTcF) > 450 msec, a complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form) or an incomplete left bundle branch block.

Excluded medications or treatment regimens

8. *(Exclusion criterion removed with Protocol Amendment 14)*
9. Have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support within one week or pegylated G-CSF within two weeks before the Screening Visit.
10. Have received a cumulative dose of corticosteroid ≥ 150 mg (prednisone or equivalent doses of corticosteroids) within two weeks before the first infusion.
11. *(Exclusion criterion removed with Protocol Amendment 13).*

Surgery/procedures

12. Major surgery within six weeks or open biopsy within seven days before drug infusion.
13. Plan for any major surgery during treatment period.

14. Patients not willing or able to have a pre-study tumor biopsy taken. In the Dose Escalation part, the screening biopsy can be omitted if archived material is available. In the Cohort Expansion part, the most recent available archived sample can be used; if no biopsies are available a new biopsy must be obtained before dosing.
15. Presence or anticipated requirement of epidural catheter in relation to infusions (within 48 hours before and after dose of study drug).

Central nervous system

16. Any history of intracerebral arteriovenous malformation, cerebral aneurysm, brain metastases or stroke.
    - Transient ischemic attack > 1 month prior to screening is allowed.

Prior therapy

17. Any anti-cancer therapy including; small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug within five half-lives before first infusion. For anti-cancer therapies with half-lives greater than 8 days, a washout period of at least 28 days is acceptable.
18. Prior treatment with bevacizumab within twelve weeks before the first infusion.
19. Any prior therapy with a conjugated or unconjugated auristatin derivative.
20. Radiotherapy within 28 days prior to first dose.
21. Patients who have not recovered from symptomatic side effects of radiotherapy or symptoms of autoimmune toxicities related to previous treatment with check-point inhibitors at the time of initiation of screening procedure.

Other cancer/metastases

22. Known past or current malignancy other than inclusion diagnosis, except for:
    - Cervical carcinoma of Stage 1B or less.
    - Non-invasive basal cell or squamous cell skin carcinoma.
    - Non-invasive, superficial bladder cancer.
    - Prostate cancer with a current PSA level < 0.1 ng/mL.
    - Breast cancer in BRCA1 or BRCA2 positive ovarian cancer patients.
    - Any curable cancer with a complete response (CR) of > 5 years duration.
23. Radiographic evidence of cavitating pulmonary lesions.
24. For the Dose Escalation part: Tumor adjacent to or invading any large blood vessel, unless approved by the sponsor Medical Officer.

    For the Cohort Expansion part: Tumor invading any large blood vessel.

Other

25. Ongoing significant, uncontrolled medical condition.

26. Presence of CTCAE grade ≥ 2 peripheral neuropathy.
27. Clinically significant active viral, bacterial or fungal infection requiring:
    - Intravenous treatment with antimicrobial therapy starting less than four weeks prior to first dose, or
    - Oral treatment with antimicrobial therapy starting less than 10 days prior to first dose.
28. Known human immunodeficiency virus seropositivity.
29. Positive serology (unless due to vaccination or passive immunization due to Ig therapy) for hepatitis B defined by:
    - Positive test for HBsAg (hepatitis B surface antigen) and/or
    - Positive test for anti-HBs and anti-HBc (antibodies to hepatitis B surface and core antigens).
30. Positive serology for hepatitis C based on test at screening.
31. Inflammatory bowel disease including Crohn's disease and colitis ulcerosa.
32. Inflammatory lung disease including moderate and severe asthma and chronic obstructive pulmonary disease (COPD) requiring chronic medical therapy.
33. Ongoing acute or chronic inflammatory skin disease.
34. Ophthalmological:
    - Active ocular surface disease at baseline (based on ophthalmological evaluation).
    - History of cicatricial conjunctivitis (as evaluated by an ophthalmologist).

8.3.3 Patient Allocation Procedure

Allocation of patients in both Dose Escalation and Cohort Expansion parts will be controlled by the CRO.

When a potential patient is identified at a site, the site personnel must contact the CRO for allocation in accordance to Section 8.4.12.2. If there is an opening in the currently enrolling cohort, the site will be given approval to start the screening process.

If there is no opening in the currently enrolling cohort, the CRO will place the patient on a list of potential patients. If another patient fails the screening process, the CRO will alert the site that has the next patient on the waiting list. If the patient is still eligible, the site will be given approval to start the screening process.

8.3.4 Withdrawal and Replacement of Patients

8.3.4.1 Criteria for Patient Withdrawal from Treatment

Dose Escalation Part:

Patients will be withdrawn from treatment for the following reasons:

- DLT (see Section 8.4.13 for specification and exception)
- > 2 dose reductions due to recurrent toxicities possibly related to tisotumab vedotin (HuMax-TF-ADC) (see Sections 8.4.5, 8.4.6 and 8.4.8)
- Dose delay of more than 2 weeks due to toxicity possibly related to tisotumab vedotin (HuMax-TF-ADC)
- Pregnancy
- Patient choice

Cohort Expansion Part:

Patients will be withdrawn from treatment for the following reasons:

- CTCAE grade ≥ 3 macular-papular skin rash
- TEN, Steven Johnson and CTCAE grade ≥ 3 cutaneous vasculitis
- CTCAE grade ≥1 treatment-related bullous dermatitis or skin bullae (blister) ≥ 0.5 cm
- CTCAE grade 4 peripheral neuropathy
- CTCAE grade 4 neutropenia for a minimal duration of seven days
- CTCAE grade 4 febrile neutropenia (with a single temperature of > 38.3°C or a sustained temperature of ≥ 38 °C for more than one hour)
- CTCAE grade 4 thrombocytopenia
- Major bleeding (as defined in Section 10.11)
- CTCAE grade 4 IRR
- CTCAE grade ≥ 3 QTcF interval prolongation (≥ 501 msec on at least two separate ECGs)
- First recurrence of CTCAE grade ≥ 3 conjunctivitis (despite dose reduction, see Section 8.4.8)
- Third occurrence of CTCAE grade ≤ 2 keratitis (despite dose reductions, see Section 8.4.8)
- First occurrence of CTCAE grade ≥ 3 keratitis
- Ophthalmological evaluation reveals conjunctival/corneal scarring
- Any grade of symblepharon
- Any grade of fluorescent patches or conjunctival ulceration that does not stabilize or improve after dose reduction
- Any dose delay related to ocular toxicity exceeding 12 weeks following discussion with the Genmab Medical Officer

- > 2 dose reductions due to recurrent toxicities possibly related to tisotumab vedotin (HuMax-TF-ADC)
- Dose delay of more than 2 weeks due to toxicity possibly related to tisotumab vedotin (HuMax-TF-ADC) (except for dose delays due to neuropathy, skin rash, keratitis and conjunctivitis)*
- Pregnancy
- Patient choice
- Investigator or sponsor decision

* This exception is due to the fact that decrease to CTCAE grade 1 in intensity for neuropathy, skin rash, keratitis and conjunctivitis may last for more than 2 weeks.

8.3.4.2 Criteria for Patient Withdrawal from the Study

Patients will be withdrawn from the study (Dose Escalation or Cohort Expansion parts) at any time for any of the following reasons:

- Patient choice
- Investigator or sponsor decision
- Disease progression
- Initiation of new anti-cancer treatment
- Lost to follow-up
- Intercurrent illness that precludes further participation or requires a prohibited concomitant treatment

8.3.4.3 Evaluations at Withdrawal from Treatment

When a patient withdraws from treatment, he/she should return for follow-up visits and the End of Treatment page must be filled in.

8.3.4.4 Evaluations at Withdrawal from the Study

When a patient withdraws from the study, investigators should attempt to obtain information and perform an EOS Visit as soon as possible and prior to initiation of new treatment. In addition, a Safety Follow-up Visit must be performed at least 30 days following the last dose of IMP. The EOS Visit will include most assessments performed at the Screening Visit, and response assessments (see Section 9.1.5 for the EOS Visit in the Dose Escalation part and Section 9.2.5 for the EOS Visit in the Cohort Expansion part). The Safety Follow-up Visit should only be performed if the patient withdraws before attending Follow-up Visit 1. Only SAEs will be assessed at the Safety Follow-up Visit, as well as any new anti-cancer treatment, if applicable, in the Cohort Expansion part.

For patients considered as lost to follow-up, the investigator should make an effort (at least one phone call or one written message to the patient), and document his/her effort (date and summary of the phone call or copy of the written message in the source documents), to

complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the patient, must be recorded in the source documents. The primary reason for withdrawal will be recorded in the eCRF.

8.3.4.5 Replacement of Patients

Patients who discontinue the study during the first cycle (21 days) of the Dose Escalation part for reasons other than a DLT should be replaced. Patients in the Cohort Expansion part who discontinue the study without receiving dose on first cycle for whatever reason should be replaced; patients who withdraw after the first dose of the first cycle in the Cohort Expansion will not be replaced.

Patients who are withdrawn after the first cycle of the Dose Escalation part or during the Cohort Expansion part will not be replaced. However, sufficient number of patients will be included to ensure the minimum sample size defined (see Section 12.9).

8.4 Treatment

The Dose Escalation part is a FIH study and it must be run in phase I units with cardiopulmonary resuscitation rescue equipment available and fast access to Emergency units. The Cohort Expansion part is considered a phase II study and the sites do not need to be phase I units. Throughout the infusion patients will be under surveillance by study personnel. The physician supervising the study drug infusion must be readily accessible for assistance during the day of infusion.

Tisotumab vedotin (HuMax-TF-ADC) is an antibody drug conjugate composed of an IgG1 human monoclonal antibody (HuMax-TF) chemically conjugated via a protease cleavable vc linker to the drug MMAE.

Tisotumab vedotin (HuMax-TF-ADC) is presented as a lyophilized cake for reconstitution in water for injection and is intended for dosing by the intravenous route by infusion after dilution in physiological saline solution. During the Dose Escalation part the drug product (Batch #3C001) will be used.

8.4.1 Treatments Administered

The final composition of the drug product after reconstitution is 10 mg/mL tisotumab vedotin (HuMax-TF-ADC) formulated in a mixture of histidine, sucrose, mannitol at pH 6.0.

The investigator must ensure that the study drug will be used only in accordance with the protocol.

Tisotumab vedotin (HuMax-TF-ADC) will be administered as an intravenous infusion on Day 1 of each cycle (one treatment cycle is 21 days). Each patient's dose will be calculated based on the patient's weight (measured at the particular dosing visit; see Section 10.3) rounded to the nearest kilogram, i.e., assigned cohort dose in mg/kg × body weight in kg. For patients whose body mass index (BMI) is greater than 30 kg/m^2, the investigator should use a weight that, based on the patient's height, corresponds to a maximum BMI of 30.

The dose is calculated according to the following formula if BMI is greater than 30 kg/m^2:

*Dose (mg) = x (mg/kg) * 30 (kg/m^2)* height (m) * height (m)*

Tisotumab vedotin (HuMax-TF-ADC) will be administered over a minimum of one hour in the Dose Escalation part and over a minimum of 30 minutes in the Cohort Expansion part. If infusion-related events emerge, refer to Section 8.4.4. The infusion is complete when the infusion line has been flushed with minimum 15 mL saline. Preventive eye therapy should be administered in relation to infusions as detailed in Section 8.4.8.

8.4.2 Study Treatment Preparation

The dose of tisotumab vedotin (HuMax-TF-ADC) for administration must be prepared by the site pharmacy using aseptic technique. Tisotumab vedotin (HuMax-TF-ADC) will be supplied to the site/pharmacy as bulk supply cartons.

The IMP will be supplied in vials containing 40 mg of tisotumab vedotin (HuMax-TF-ADC) as lyophilized powder. The powder should be reconstituted with 4 mL water for injection leading to a 10 mg/mL solution.

The reconstituted tisotumab vedotin (HuMax-TF-ADC) should be diluted into 0.9% NaCl 100 mL infusion bag according to the dose assigned to the patient.

Tisotumab vedotin (HuMax-TF-ADC) lyophilized vials should be stored in a refrigerator at 2°C to 8°C.

The infusion must be completed within 24 hours after the tisotumab vedotin (HuMax-TF-ADC) vials have been reconstituted. An in-line filter must be used for the infusion. The entire 100 mL infusion volume from the prepared infusion bag needs to be administered, no dead volume is provided.

Please refer to the Pharmacy Manuals for instructions on storage, preparation and infusion. Labeling will be in accordance with the EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products, and any other applicable local regulatory requirements.

8.4.3 Study Treatment Storage and Accountability

It is forbidden to use investigational drug material for purposes other than as defined in this protocol.

8.4.3.1 Study Treatment Storage

Tisotumab vedotin (HuMax-TF-ADC) will be stored at 2-8°C in a secure area with restricted access.

8.4.3.2 Study Treatment Accountability

The study drug must exclusively be used for the investigation specified in this protocol and it will only be accessible to authorized staff. The investigator or designee must confirm and document the receipt of the study drug.

Vials must be kept at the pharmacy. Throughout the study, all used and unused material will be accounted for. Documented destruction of drugs and containers should be coordinated at the clinical site. One copy of the destruction certificate must be kept in the investigator's file and the other copy must be sent to the sponsor representative.

8.4.4 Treatment of Infusion-Related Reactions

Infusion-related reactions have been observed with other MMAE-ADCs. One IRR including skin rash and swelling of eyes and lips was observed during non-clinical studies in a female monkey following a second dose of tisotumab vedotin (HuMax-TF-ADC) 3 mg/kg. No IRRs were observed in this animal following the third or fourth dose administration of IMP. Infusion-related reactions have been observed in patients treated with tisotumab vedotin (HuMax-TF-ADC), but the majority of the reactions have been mild to moderate (data cut-off date 16 Aug 2017). Please refer to the Investigator's Brochure for more information.

- Patients should be monitored during infusion.
- If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. The infusions may be restarted at the investigator's discretion.
- Patients who have experienced prior infusion-related CTCAE grade ≥ 3 reactions in the study should be pre-medicated before all subsequent infusions with antihistamine and/or acetaminophen and/or corticosteroid at the investigator's discretion.
- If anaphylaxis occurs, administration of study drug should be discontinued immediately and permanently and appropriate medical therapy should be administered.

8.4.5 Dose Modification and Mitigation Plan for Skin Toxicity

- Ongoing, acute or chronic inflammatory skin disease is an exclusion criterion in this study (see Section 8.3.2).
- Frequent assessments of skin should be performed during Cycles 1 and 2 of the Dose Escalation part:
  - At Days 1, 2, 4, 8, 11, and 15 of each three-week cycle.
- Assessment of skin during the remaining cycles of the Dose Escalation part will be performed on Day 1 in each cycle before dosing.
- During the Cohort Expansion part, assessments of skin should be performed during Cycles 1 and 2:
  - At Days 1 and 15 of each three-week cycle.
- Assessment of skin during the remaining cycles of the Cohort Expansion part will be performed on Day 1 in each cycle before dosing.
- Patients' information to include information about potential skin toxicity and, for the Dose Escalation part, advise the patients to contact the investigator and/or the site dermatologist in case of skin rash, pruritus or bullae. For the Cohort Expansion part, due to benign skin toxicity profile observed in the Dose Escalation part, the visit to dermatologist is optional.
- Investigators will be trained in skin monitoring and action to findings.
- Dose adjustment for skin toxicity should be managed as follows:

- For CTCAE grade 1 macular-papular skin rash: Continue dosing of tisotumab vedotin (HuMax-TF-ADC) as planned, treat with a potent topical steroid (betamethasone valerate or equivalent) once daily for up to one week, facial areas with a moderate topical steroid (Hydrocortisone butyrate 0.1% or equivalent) twice daily for up to one week; thereafter every other day for a maximum of three weeks.
- For CTCAE grade 2 macular-papular skin rash: Postpone dosing of tisotumab vedotin (HuMax-TF-ADC) until skin rash has decreased to grade 1, then continue dosing of tisotumab vedotin as planned. Treat the skin rash with a potent topical steroid (betamethasone valerate or equivalent) once daily for up to one week; facial areas with a moderate topical steroid (Hydrocortisone butyrate 0.1% or equivalent) twice daily, followed by dosing once every other day for a maximum of three weeks.
- For CTCAE grade ≥ 3 macular-papular skin rash: Stop dosing (patient withdrawal) and treat the skin rash with a potent topical steroid (betamethasone valerate or equivalent) once daily for up to one week, followed by dosing once every other day for a maximum of three weeks.
- Vesicular skin reaction: postpone dosing until recovery and continue on half dose until the end of treatment period.

- Withdrawal criteria for skin toxicity:
  - Patients with CTCAE grade ≥ 3 macular-papular skin rash (covering ≥ 30% of body surface area [BSA]).
  - Patients with TEN, Steven Johnson and CTCAE grade ≥ 3 cutaneous vasculitis.
  - Patients with CTCAE grade 1 treatment-related bullous dermatitis or skin bullae (blister) ≥ 0.5 cm.

8.4.6 Mitigation Plan for Mucositis

From implementation of Protocol Amendment 6:

- Patients with CTCAE grade 3 mucositis: hold dose until mucositis improves to grade 2 and treat according to local practice.
- Withdrawal criteria for mucositis:
  - Patients with CTCAE grade ≥ 4 mucositis: the patient should be withdrawn from treatment.

8.4.7 Dose Modification for Peripheral Neuropathy and Neutropenia

Peripheral neuropathy should be managed using a combination of dose delay and reduction to 2/3 of the initial dose:

- For new or worsening CTCAE grade 2 or 3 neuropathy: hold dose until neuropathy improves to grade ≤ 1, and then restart at 2/3 of the initial dose until end of study treatment.

- For CTCAE grade 4 peripheral neuropathy: stop dosing and the patient should be withdrawn from treatment.

Neutropenia should be managed by dose delays and dose reductions:

- Dosing should be held for grade 3 or 4 neutropenia until resolution to CTCAE grade ≤ 2.
- Growth factor support should be considered for subsequent cycles in patients who experience CTCAE grade 3 or 4 neutropenia.
- In patients with recurrent CTCAE grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of study drug to 2/3 of the initial dose until end of study treatment may be considered after discussion with the Genmab Medical Officer.

8.4.8 Dose Modification and Mitigation Plan for Ocular Adverse Events

Events of conjunctivitis and keratitis have been reported in patients treated with tisotumab vedotin (HuMax-TF-ADC). To prevent occurrence and ensure appropriate handling, events should be prevented and managed as described below.

Preventive measures for all patients:

- Use of preservative-free lubricating eye drops from the start of study treatment until the end of treatment.
- Avoid use of contact lenses while treated with tisotumab vedotin (HuMax-TF-ADC).
- Use of refrigerator-based eye cooling pads during infusion, e.g. THERA PEARL Eye Mask or similar. To be applied immediately before infusion in accordance with the instructions provided with the eye cooling pads.
- Administration of local ocular vasoconstrictor before infusion (brimonidine tartrate 0.2% eye drops or similar, 3 drops in each eye immediately prior to start of infusion; otherwise to be used in accordance with the product prescribing information). If the patient does not tolerate ocular vasoconstrictors due to adverse reactions, continued treatment with these may be stopped at the discretion of the investigator and following discussion with the Genmab Medical Officer.
- Application of steroid eye drops for 3 days from the day of infusion (dexamethasone 0.1% eye drops or equivalent, 1 drop in each eye 3 times daily for 3 days [first drop to be given before start of infusion], otherwise to be used in accordance to product prescribing information).

In case of any ocular symptoms:

<u>Conjunctivitis:</u>

Grading: All events of conjunctivitis should be graded according to both:

- Ophthalmological grading based on the objective eye-examination findings performed by the ophthalmologist.

- CTCAE grading system based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (NCI-CTCAE v4.03, 2010) assessed by the investigator.

Dose delay and dose modification:

- CTCAE grade 1 conjunctivitis: Hold dosing until the event is managed effectively by topical treatment initiated by the ophthalmologist (according to treatment guidelines below). When the event is managed effectively the patient can be re-treated with the same dose of trial drug as being administered prior to the event onset.
- CTCAE grade 2 conjunctivitis: Hold dosing. Topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event has improved to ≤ CTCAE grade 1, dosing of trial drug can be resumed at the same dose as administered prior to the event onset.
    - In case of recurrence of CTCAE grade 2 conjunctivitis, the patient should hold dosing and topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event is CTCAE grade ≤ 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
        - In case of a third occurrence of CTCAE grade 2 conjunctivitis, the patient should hold dosing and topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event is CTCAE grade ≤ 1, dosing of trial drug can be resumed at a further reduced dose (please refer to dose modification scheme below).
            - In case of ≥ fourth occurrence of CTCAE grade 2 conjunctivitis, the patient should hold dosing and topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event is CTCAE grade ≤ 1, dosing of trial drug should not be further reduced but resumed at 0.9 mg/kg.
- CTCAE grade ≥ 3 conjunctivitis: Hold dosing. Topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event has improved to CTCAE grade ≤ 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
    - If the conjunctivitis recurs at CTCAE grade ≥ 3, the patient must permanently discontinue treatment with trial drug.

<u>Keratitis:</u>

Grading: All events of keratitis should be graded according to both:

- Ophthalmological grading based on the objective eye-examination findings performed by the ophthalmologist.
- CTCAE grading system based on NCI-CTCAE criteria assessed by the investigator (CTCAE version 4.03).

Dose delay and dose modification:

- CTCAE grade ≤ 2 keratitis: Hold dosing until the event is managed effectively by topical treatment (according to treatment guidelines below) initiated by the ophthalmologist. When the event is ≤ CTCAE grade 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
    - In case of recurrence of CTCAE grade ≤ 2 keratitis, the patient should hold dosing and topical treatment (according to treatment guidelines below) should be initiated by the ophthalmologist. When the event is CTCAE grade ≤ 1, dosing of trial drug can be resumed at a further reduced dose (please refer to dose modification scheme below).
        - In case of third occurrence of keratitis CTCAE grade ≤ 2, the patient must permanently discontinue treatment with trial drug.
- CTCAE grade ≥ 3 keratitis: The patient must permanently discontinue treatment with trial drug.

Conjunctival ulceration:

If an ophthalmological evaluation reveals fluorescent patches or conjunctival ulceration of any grade:

- Hold dose until conjunctivitis/conjunctival ulceration is managed effectively by topical treatment (according to treatment guidelines below). When the event is managed effectively, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
- If symptoms do not stabilize/improve after dose reduction, the patient must permanently discontinue treatment with trial drug.

Treatment guidelines

Ocular symptom	**Treatment guideline** (The length of treatment should be decided by the local ophthalmologist)
Conjunctivitis: CTCAE grade 1	The local ophthalmologist should prescribe frequent dosing of preservative-free topical steroid drops
Conjunctivitis: CTCAE grade 2	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol
Conjunctivitis: CTCAE grade 3	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol
Keratitis: CTCAE grade 1	The local ophthalmologist should prescribe frequent dosing of preservative-free topical steroid drops

Ocular symptom	**Treatment guideline** (The length of treatment should be decided by the local ophthalmologist)
Keratitis: CTCAE grade 2	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol
Conjunctival ulceration: any grade	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol

Dose modification scheme:

Previous dose of tisotumab vedotin	**Reduced dose of tisotumab vedotin**
2.0 mg/kg	1.3 mg/kg
1.3 mg/kg	0.9 mg/kg
0.9 mg/kg	0.9 mg/kg*

**If the patient is already being treated with tisotumab vedotin (HuMax-TF-ADC) 0.9 mg/kg every 3rd week, the dose of tisotumab vedotin (HuMax-TF-ADC) should not be reduced further.*

Trial drug discontinuation criteria for ocular toxicity:

Treatment with trial drug must be permanently discontinued in case of:

- First recurrence of CTCAE grade ≥ 3 conjunctivitis (despite dose reduction)
- Third recurrence of CTCAE grade ≤ 2 keratitis (despite dose reductions)
- First occurrence of CTCAE grade ≥ 3 keratitis
- Ophthalmological evaluation reveals conjunctival/corneal scarring
- Any grade of symblepharon
- Any grade of fluorescent patches or conjunctival ulceration that does not stabilize or improve after dose reduction
- Any dose delay related to ocular toxicity exceeding 12 weeks following discussion with the Genmab Medical Officer

8.4.9 Dose Modification for QTcF Changes in the Electrocardiogram

Prolongation of QTcF interval during the study should be managed as follows:

- For CTCAE grade 1 QTcF interval prolongation (450 to 480 msec): check electrolytes (calcium, magnesium and potassium) prior to next dosing, but no dose adjustment or dosing hold is required.

- For CTCAE grade 2 QTcF interval prolongation (481 to 500 msec): hold dosing until improvement to grade 1 or lower and check electrolytes (calcium, magnesium and potassium) and substitute until normal levels; then dose can be restarted and ECGs should be performed at least every other day.

If the QTcF interval prolongation is not related to electrolyte abnormality, hold dosing until improvement to grade 1 or lower; then next infusions may be restarted at half of the initial infusion rate; ECGs should be performed at least every other day.

- For CTCAE grade 3 QTcF interval prolongation (≥ 501 msec on at least two separate ECGs): stop dosing. Then, check electrolytes (calcium, magnesium and potassium) and substitute until normal levels; ECGs should be performed at least daily; consider to obtain cardiology consult.

8.4.10 Dose Modification for Increased Liver Enzymes

From implementation of Protocol Amendment 6, in case of CTCAE grade ≥ 3 liver enzymes increase is not resolved (decreased to grade 2 or lower) at time of dosing, the site must contact Genmab Medical Officer before the next dosing of the patient, in order to decide whether there should be any dose adjustment, delay or withdrawal of the patient.

8.4.11 Precautions

Patients receiving the following therapy during and three weeks after the last treatment with tisotumab vedotin (HuMax-TF-ADC) should be monitored closely for adverse reactions:

- Drugs and substances known to be strong CYP3A4 and/or P-gp inhibitors (also excluded as concomitant medication, see Section 8.4.15.3) like boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, amiodarone, clarithromycin, verapamil[1].

8.4.12 Dose Escalation

8.4.12.1 Dose Escalation Overview

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

Decisions to escalate the dose of tisotumab vedotin (HuMax-TF-ADC) for the next cohort will be based on the safety data obtained from the 3 (+3) patients during their first treatment cycle (21 days). A DMC will evaluate all safety data (including SAEs, AEs, and laboratory data) after each cohort completes Cycle 1. All patients in a cohort must be observed for at least three weeks after the first infusion before data are sent to the DMC to review.

[1] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Based on the results presented in these safety profiles, the DMC will recommend whether it appears safe to escalate the dose. The recommendation will be discussed and confirmed by the sponsor's internal Safety committee, who will ultimately decide whether dose-escalation shall occur. In addition, the DMC will evaluate at the DMC meetings cumulative data obtained during the additional three cycles per cohort.

Patients who discontinue the study during the first cycle for reasons other than a DLT should be replaced.

For this study, the MTD will be defined as the dose level below the dose at which ≥ 2 DLTs within the six patients of one cohort are observed. The DMC and the sponsor's Safety committee may decide to implement intermediate doses below that at which ≥ 2 DLTs were identified to ensure patients safety and better define the MTD.

The DMC and the sponsor's Safety committee will, based on the Dose Escalation part, determine the dose level to be used in the Cohort Expansion part including approximately 169 patients.

8.4.12.2 Dose-escalation Rules

Each cohort will start with three patients. If an unacceptable toxicity is observed during the first treatment cycle, the cohort for the current dose level will be expanded to include an additional three patients.

The classic 3+3 design will be implemented as follows:

- Three patients are allocated per new dose level until a DLT is observed.
- In each cohort, a minimum of ten days between administration of first dose in patient 1 and patient 2, and minimum of one day between the subsequent patients will be implemented.
- All patients in a cohort must be observed for at least three weeks after the first infusion before data are sent to the DMC to review and decide on dose escalation.
- If a DLT is observed within the first cycle, the cohort on the corresponding dose level will be expanded with three additional patients. Depending on the nature of the DLT, the DMC may require that at least one patient of the additional three patients to be included at the same dose level should have the same cancer type as the patient who had the DLT.
- If no other DLTs are identified the study will continue escalation to next dose level.
- If one additional DLT (i.e. ≥ 2 DLTs within the six patients) is observed on the same dose level, additional patients will not be enrolled at that dose level. The dose will be de-escalated until a dose level where three patients with no observed DLTs or, six patients have been treated with ≤ 1 instance of DLT observed. This will be the MTD.

In order to adequately assess the safety of the mixed population in this study, dose cohorts will be partially stratified as follows:

Table 5: Number of Different Cancer Types Represented in Each Dose Cohort, Depending on Cohort Size (Dose Escalation Part)

No. of patients in cohort	Number of different cancer types represented in the cohort
3	≥ 2
6	≥ 3*

**Depending on the nature of the safety signal observed, the DMC may require that at least one patient of the additional three patients to be included at the same dose level should have the same cancer type as the patient who had the DLT.*

8.4.13 Dose Limiting Toxicities for the Dose Escalation Part of the Study

For the purpose of dose-escalation, DLTs will be collected and assessed for the first cycle (21 days) of each cohort. DLTs must be reported to the sponsor within 24 hours. Causality for DLTs will be assessed by the sponsor in collaboration with the DMC.

DLTs include the following AEs at least possibly related to tisotumab vedotin (HuMax-TF-ADC):

- Grade 4 neutropenia (i.e., ANC < 0.5 $\times 10^9$ cells/L) for minimal duration of seven days.
- Grade 3 and 4 febrile neutropenia (i.e., ANC < 1.0 $\times 10^9$ cells/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour).
- Grade 4 thrombocytopenia (≤ 25.0 $\times 10^9$ platelets/L).
- Grade 3 thrombocytopenia associated with bleeding episodes.
- Major bleeding (as defined in Section 10.11).
- Stevens Johnson syndrome, TEN, grade ≥ 3 cutaneous vasculitis.
- Grade 3 neuropathy (not improving to grade 1 within 3 weeks following stop of dosing) and grade 4 neuropathy.
- Grade 3 infusion-related AEs that do not resolve to grade 1 or baseline within 24 hours.
- Grade 4 infusion-related events including anaphylaxis.
- Any grade ≥ 3 non-hematological AEs which occur during the first treatment cycle and are at least possibly study drug related, excluding non-hematological laboratory abnormalities that have no clinical consequences and resolve within 48 hours.
- Grade ≥ 3 diarrhea and/or vomiting persisting for more than 48 hours with optimal medical management.
- Grade ≥ 3 nausea (not disease-related) lasting 3 days or more with optimal medical management.

At the DMC meetings following each cohort, safety data for the specific cohort as well as cumulative safety data (SAEs, AE and laboratory data) for all cohorts will be evaluated for identification of any safety signals and actions will be recommended by the DMC. Following each DMC meeting, an internal Safety committee meeting will be held comprising Heads of

Drug Safety, Regulatory, Clinical Development and Medical to discuss and confirm actions recommended by the DMC.

From implementation of Protocol Amendment 6, depending on the nature of the DLT and patient status, the DMC and sponsor's Safety committee in agreement with the investigator may allow a patient with a DLT to continue on the study on a reduced dose.

8.4.14 Data Evaluation for the Cohort Expansion Part

During the Cohort Expansion part, a pre-planned safety evaluation is scheduled after the first ten patients (across indications) are followed for at least one cycle. Based on cumulative overall safety data, including all reported AEs, SAEs, withdrawals and laboratory data, the DMC can propose and the sponsor's Safety committee can endorse the following actions:

- whether the protocol should continue unchanged,
- whether the protocol should be modified,
- whether the dose be reduced,
- whether dosing and study entry should be held for already included patients,
- whether additional patients should be included, or
- whether the study should be discontinued permanently.

Also, based on this safety evaluation, opening of the remaining three indications (SCCHN, NSCLC and esophageal cancer) can be determined. A second safety evaluation is pre-planned when 30 patients have been dosed and followed for at least one cycle.

In the cervical and endometrial cancer indications, efficacy will be evaluated at an interim analysis after enrolling 14 of the pre-planned 30 patients in each of these indications. After a minimum of 6 weeks of therapy, if no responder is observed among the first 14 enrolled patients, then pending DMC recommendation and approval by the sponsor's Safety committee, no further patients are to be enrolled in the relevant indication.

Where applicable, regulatory authorities IECs/IRBs will be notified of any actions taken with the study.

8.4.15 Prior and Concomitant Therapy

8.4.15.1 Prior Therapy

The following therapies must be recorded as applicable and taken into account for the evaluation of the inclusion and exclusion criteria:

- Any prior anti-cancer treatment regimens.
- Any systemic therapy administered within three months prior to screening.

Administration of prior therapies must be reported in the appropriate section of the eCRF along with dates of administration and reasons for use.

8.4.15.2 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" (Section 8.4.15.3). Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dates of administration and reasons for use.

8.4.15.3 Excluded Concomitant Medications

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The sponsor must be notified if a patient receives any of these during the study.

- Any investigational anti-cancer therapy.
- Drugs and substances known to be strong CYP3A and/or P-gp inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, amiodarone, clarithromycin, verapamil) should not be administered during the study period.

8.4.15.4 Treatment Compliance

Tisotumab vedotin (HuMax-TF-ADC) will be administered by study site personnel, who will monitor patient compliance.

8.4.15.5 Assignment to Treatment

This is an open-label study. Study participation begins once written informed consent is obtained.

After obtaining informed consent, patients will be given a screening number before they undergo any screening procedure. A screening number consists of the letter "S" followed by the study number and subsequently a three- or four-digit number that uniquely identifies a patient at a screening visit. For example, a screening number in this study could be "S701034".

Subjects who have complied with all selection criteria will receive a patient number upon enrolment in the study. A patient number consists of the study number combined with a three-or four-digit number that uniquely identifies a patient during the study. For example, patient 12 in this study would be uniquely identified by the combined code "701012".

A master log of all consented patients will be maintained at the sites and will document all screening failures (i.e., patients who are consented but do not meet the study eligibility criteria) including the reason for screening failure.

9. STUDY EVALUATIONS

Study evaluations by visit are detailed in the Schedules of study procedures in Table 1 for the Dose Escalation part and in Table 2 for the Cohort Expansion part. A description of the methods of assessments is provided in Section 10.

All patients who are assigned a patient number and receive any study drug will be followed according to the protocol regardless of the number of doses received, unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations, and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviations and any study-specific eCRF or logs designated for capturing protocol deviations, if applicable for the study. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IEC/IRB.

Patients will be instructed to call the study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

9.1 Dose Escalation Part

9.1.1 Dose Escalation: Screening (Visit 0)

All screening procedures must be performed within 21 days before the first dose of tisotumab vedotin (HuMax-TF-ADC) on Day 1 of Cycle 1 (C1-V1), except for the CT-scan that may be performed within four weeks before C1-V1. The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations.

A patient may be rescreened one time only. A rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

9.1.2 Dose Escalation: Treatment

The investigator must have evaluated the patient's eligibility and confirm receipt of sponsor decision and patient number before the patient's first infusion. This form will have to be validated by the sponsor and/or designee and will serve to assign the patient number.

Tisotumab vedotin (HuMax-TF-ADC) will be administered every 21 days, on Day 1 of each treatment cycle. Dose-escalation to MTD is anticipated to involve approximately eight dose levels with an anticipated maximal exposure of 2.6 mg/kg.

The patients will receive four cycles (doses) of tisotumab vedotin (HuMax-TF-ADC) at three-week intervals. Thus, the treatment period will last for twelve weeks, or until disease progression.

For the first two infusions the patient must stay hospitalized the first 24 hours and be monitored including vital signs and general assessment for any reactions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Patients requiring treatment for infusion-related reactions should be monitored until the resolution of the event.

For all subsequent infusions the patient should be closely monitored including vital signs and general assessment for at least 2 hours following administration of tisotumab vedotin (HuMax-TF-ADC) in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Patients requiring treatment for infusion-related reactions should be monitored until the resolution of the event.

9.1.2.1 Dose Escalation Cycles 1 and 2

During Cycles 1 and 2 of the Dose Escalation part, six study visits will be performed on Days 1, 2, 4, 8, 11 and 15 of each cycle, with a visit window of ± 1 day (except for the visit on Day 2).

On Cycles 1 and 2, the patient shall stay hospitalized the first 24 hours after the infusion and be discharged the following day after assessments and at the discretion of the investigator.

9.1.2.2 Dose Escalation Cycles 3 and 4

During Cycles 3 and 4 of the Dose Escalation part, three-weekly study visits will be performed on Days 1 (± 3 days), 8 (± 1 day), and 15 (± 1 day) of each cycle.

After four cycles, if there is evidence of the patient benefitting from treatment, there is an option to continue in the study for up to a maximum of eight additional cycles (24 weeks) or until unacceptable toxicity according to protocol, at the discretion of the treating physician after agreement with Genmab on the patient status.

9.1.2.3 Dose Escalation Cycles 5 to 12

For patients who continue in the study for additional cycles in the Dose Escalation part, weekly study visits will be performed on Days 1 (± 3 days), 8 (± 1 day), and 15 (± 1 day) of each cycle (Cycles 5 to 12). In addition, a CT-scan will be performed 21 days (± 3 days) after Day 1 of Cycle 12.

At the end of this period, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or PD is observed.

9.1.3 Dose Escalation Follow-up Visits (FU1 to FU4)

If the patient withdraws from treatment or completes all twelve cycles, he/she will continue follow-up visits every six weeks (± 7 days) until PD, other treatment is initiated or the patient withdraws from the study due to other reasons, for a maximum of 24 weeks.

9.1.4 Dose Escalation Unscheduled Visit (U1 to UX)

If judged necessary by the investigator the patient can be called in for unscheduled visit(s). The reason for the visit and visit date must be recorded in the eCRF.

During an unscheduled visit the investigator will assess AEs and record concomitant medication. Additional study assessments can be performed at the investigator's discretion. To monitor patient safety the investigator may request additional blood samples.

9.1.5 Dose Escalation End of Study Visit (EOS)

If a patient withdraws from the study, the EOS Visit should be performed as soon as possible after withdrawal. If a patient completes all the follow-up visits, the EOS Visit should be performed four weeks after Follow-up Visit 4.

9.1.6 Dose Escalation Safety Follow-up Visit (SFU)

Patients who withdraw from the study before Follow-up Visit 1 will return for a Safety Follow-up Visit 30 days (+ 14 days) after the last IMP dosing. In the Safety Follow-up Visit, only SAEs will be assessed.

9.2 Cohort Expansion Part

9.2.1 Cohort Expansion: Screening (Visit 0)

All screening procedures must be performed within 21 days before the first dose of tisotumab vedotin (HuMax-TF-ADC) on Day 1 of Cycle 1 (C1-V1), unless otherwise specified (see Table 2). The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations.

A patient may be rescreened one time only. A rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

9.2.2 Cohort Expansion: Treatment

The investigator must have evaluated the patient's eligibility and signed the Screening Evaluation Form before the patient's first infusion. This form will have to be validated by the sponsor and/or designee and will serve to assign the patient number.

In the Cohort Expansion part of the study approximately 169 patients will receive four cycles of tisotumab vedotin (HuMax-TF-ADC) once q3wk at the dose determined from the Dose Escalation part (2.0 mg/kg). Tisotumab vedotin (HuMax-TF-ADC) will be administered every 21 days, on Day 1 of each treatment cycle. Preventive eye therapy should be administered in relation to infusions as detailed in Section 8.4.8.

Extended treatment until disease progression (with a maximum of twelve cycles) or unacceptable toxicity will be available according to protocol. As in the Dose Escalation part of the study, doses will be given at three-week intervals, and the treatment period will last for a maximum of 36 weeks.

The patient should be closely monitored including vital signs and general assessment for at least two hours following administration of tisotumab vedotin (HuMax-TF-ADC) in a setting with access to resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen).

Patients requiring treatment for infusion-related reactions should be monitored until the resolution of the event.

9.2.2.1 Cohort Expansion Cycles 1 to 4

During Cycles 1 to 4 of the Cohort Expansion part, three-weekly study visits will be performed on Days 1, 8 and 15 of each cycle, with a visit window of ± 1 day.

After four cycles, if there is evidence of the patient benefitting from treatment, extended treatment until disease progression (with a maximum of twelve cycles) or unacceptable toxicity will be available according to protocol, at the discretion of the treating physician. As in the Dose Escalation part of the study, doses will be given at three-week intervals, and the treatment period will last for a maximum of 36 weeks.

9.2.2.2 Cohort Expansion Cycles 5 to 12

For patients who continue in the study for additional cycles in the Cohort Expansion part, three-weekly study visits will be performed on Days 1 (± 3 days), 8 (± 1 day), and 15 (± 1 day) of each cycle (Cycles 5 to 12). In addition, a CT-scan will be performed 21 days (± 3 days) after Day 1 of Cycle 8.

At the end of this period, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or PD is observed.

9.2.3 Cohort Expansion Follow-up Visits (FU1 to FU4)

If the patient withdraws from treatment or completes all twelve cycles, he/she will continue follow-up visits every six weeks (± 7 days) after last treatment cycle, until PD, other treatment is initiated or the patient withdraws from the study due to other reasons, for a maximum of 24 weeks.

9.2.4 Cohort Expansion Unscheduled Visit (U1 to UX)

If judged necessary by the investigator the patient can be called in for unscheduled visit(s). The reason for the visit and visit date must be recorded in the eCRF.

During an unscheduled visit the investigator will assess AEs and record concomitant medication. Additional study assessments can be performed at the investigator's discretion. To monitor patient safety the investigator may request additional blood samples.

An unscheduled visit may also be used to collect information about the optional tumor biopsy obtained three weeks after last dosing (optional) or to document a repeat CT-scan to confirm response.

9.2.5 Cohort Expansion End of Study Visit (EOS)

If a patient withdraws from the study, the EOS Visit should be performed as soon as possible after withdrawal. If a patient completes all the follow-up visits, the EOS Visit should be performed four weeks after Follow-up Visit 4.

9.2.6 Cohort Expansion Safety Follow-up Visit (SFU)

Patients who withdraw from the study before Follow-up Visit 1 will return for a Safety Follow-up Visit 30 days (+ 14 days) after the last IMP dosing. In the Safety Follow-up Visit, only SAEs, as well as any new anti-cancer treatment, if applicable, will be assessed.

10. METHODS OF ASSESSMENT

Study procedures will be performed on the study dates noted in Table 1 for the Dose Escalation part and in Table 2 for the Cohort Expansion part. A description of the different assessments is provided below.

10.1 Demographics

Date of birth, ethnic origin and gender will be recorded in the eCRF.

10.2 Medical History

Any relevant past and all current diseases will be recorded in the eCRF including staging (TNM staging system). In addition, all prior cancer treatment regimens will be recorded. Non-serious AEs (signs, symptoms and diagnosis) occurring between Visit 0 (Screening) and C1-V1 should be recorded as Medical History. For patients with cervical cancer and SCCHN, the most recent PAP smear result will be reported.

SAEs should be reported from signing informed consent both on the eCRF AE and on the SAE reporting form (as described in Section 11.3.7).

10.3 Height and Weight

Height (without shoes) must be measured at Visit 0 (Screening) and recorded in the eCRF rounded to nearest centimeter. Body weight (without overcoat and shoes) will be measured at Visit 0 (Screening), at Day 1 of each cycle, as part of the dose calculation, and at EOS, and will be recorded in the eCRF rounded to nearest kilogram. If body weight is assessed three days or less before the day of the planned dosing, this value can be used and is the weight recorded in the eCRF. In the Cohort Expansion part, the allowed window for body weight assessment is seven days or less before the day of the planned dosing.

10.4 Physical Examination

A general physical examination should include general appearance and the following body systems: lymph nodes, mouth and throat (non-tumor bearing parts), lungs, cardiovascular system, abdomen, extremities, musculoskeletal system, neurological system and skin (for assessment of skin reactions refer to Section 10.12). The outcome of the physical examination must be recorded in the eCRF.

10.5 Vital Signs

Vital signs should be recorded in the eCRF including 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 24 hours after end of infusion of the two first infusions (Dose Escalation part only) and until 2 hours after the remaining infusions, as indicated in Table 6 and Table 7 for the Dose Escalation and Cohort Expansion parts, respectively.

Table 6: Vital Signs During the Dose Escalation Part

Cycle 1 and Cycle 2 Day 1	Cycle 3 to Cycle 12 Day 1
Pre-infusion (including weight)	Pre-infusion (including weight)
15 min after start of infusion (± 5 min)	15 min after start of infusion (± 5 min)
30 min after start of infusion (± 5 min)	30 min after start of infusion (± 5 min)
45 min after start of infusion (± 5 min)	45 min after start of infusion (± 5 min)
1 hour after start of infusion (± 5 min)	1 hour after start of infusion (± 5 min)
At the end of infusion (± 5 min)	At the end of infusion (± 5 min)
10 min after end of infusion (± 5 min)	10 min after end of infusion (± 5 min)
30 min after end of infusion (± 5 min)	30 min after end of infusion (± 5 min)
1 hour after end of infusion (± 5 min)	1 hour after end of infusion (± 5 min)
2 hours after end of infusion (± 15 min)	2 hours after end of infusion (± 15 min)
6 hours after end of infusion (± 30 min)	
12 hours after end of infusion (± 1 hour)	
24 hours after end of infusion (± 1 hour)	

If infusion lasts for more than 1 hour, vital signs should be assessed every 15 minutes (± 5 minutes) for the remaining duration of infusion.

Table 7: Vital Signs During the Cohort Expansion Part

Cycle 1 and Cycle 2 Day 1	Cycle 3 to Cycle 12 Day 1
Pre-infusion (including weight)	Pre-infusion (including weight)
30 min after start of infusion (± 5 min)	
At the end of infusion (± 5 min)	At the end of infusion (± 5 min)
30 min after end of infusion (± 5 min)	
1 hour after end of infusion (± 5 min)	
2 hours after end of infusion (± 15 min)	2 hours after end of infusion (± 15 min)

If infusion lasts for more than 30 minutes, vital signs should be assessed every 30 minutes (± 5 minutes) for the remaining duration of infusion.

10.6 Electrocardiogram

ECGs will be recorded digitally at the sites by using the standard 12-leads. One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before each infusion of the study drug, in accordance with the ECG Specifications Manual. The digital ECGs will be transmitted from the sites electronically to a central laboratory for measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable.

For the ECG recordings, the patients must be resting and in a supine position for at least 10 minutes. Any irregularity observed or occurring during the ECGs (e.g., vomiting, cough) should either induce a repeat of the ECG or be annotated on the eCRF with the description and time of the occurrence.

10.7 Computerized Tomography

All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed during screening. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion. In the Cohort Expansion part only, in patients with SCCHN, an additional CT-scan of neck will be performed during screening.

Up to five target lesions (maximum two per organ) will be defined at screening and these must be followed throughout the study. Non-target lesions will also be assessed throughout the study.

Scans will be repeated every six weeks (at the end of every 2nd cycle) during the study period. If reduction of target lesions ≥ 30% in size is observed a repeat CT-scan will be performed after four weeks to confirm the response. CT-scans can be performed up to seven days before Day 1 of the relevant cycle to ensure result to be available before subsequent dosing.

For example, if a patient shows response at C3V1, a repeat CT-scan should be taken four weeks later (approximately at C4V2). The protocol next planned CT-scan would be C5V1 (-1 week), i.e., the repeat CT-scan would be performed one week earlier than the next planned CT-scan. In this case, the C5V1 CT-scan can be omitted and the next CT-scan would be at C7V1.

Additional CT-scans may be performed at the investigators discretion to confirm response or new symptoms. In this case the investigator must choose the imaging technology based on the clinical indication.

MRI can be performed instead of CT-scan if the patient is allergic to iodine contrast or at the discretion of the investigator, after approval of the sponsor.

For the Dose Escalation part the reading of the surveys will be done by a radiologist. Sites should attempt to maintain the same radiologist throughout the study. The overall interpretation of the evaluation shall be recorded in the eCRF and a copy of the evaluation reports should be kept in the patient's file.

In the Cohort Expansion part the scans will be sent for central reading and archiving.

10.8 ECOG Performance Status

The ECOG performance status scale will be used and will be assessed by the investigator at screening, on Day 1 of each cycle, and at the EOS Visit.

10.9 Adverse Events

AEs will be assessed and reported at each visit. AEs will be graded according to the NCI-CTCAE version 4.03 (NCI-CTCAE v4.03, 2010).

SAEs and non-serious grade 3 AEs will be reported from the investigational site to the sponsor within 24 hours. In addition, all non-serious grade 2 ocular AEs must be reported from the investigational site to the sponsor within 24 hours. eCRFs will be supplied to ensure fast collection of AEs.

Weekly Safety/Medical meetings will be held to evaluate all AEs and laboratory data and follow-up information obtained during the previous week.

Further details on AEs monitoring and reporting are provided in Section 11.

10.10 Concomitant Medication

Any medication or therapy other than the study drug is considered concomitant medication and should be recorded in the eCRF with the following information:

- Start date.
- Route of administration.
- Stop date of administration or ongoing at study termination.
- Indication/reason for use.

The total daily dose should be filled in whenever possible.

Recording period for concomitant medication will start from Visit 0 (Screening) until the EOS Visit.

Pre-infusion medication is entered on a separate eCRF page.

10.11 Bleeding Assessments

Major bleeding is defined as any of the following conditions according to the International Society on Thrombosis and Haemostasis (Shulman and Kearon, 2005):

- Fatal bleeding; and/or
- Symptomatic bleeding in critical area organ, such as intracranial, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or
- Bleeding causing a drop in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or bleeding leading to transfusion of two or more units of whole blood or red cells.

Minor bleeding includes:

- Cutaneous bleeding, nose bleeding, oral cavity bleeding, menorrhagia, spontaneous muscle hematomas without compartment syndrome, grade 1 and 2 hematuria, and excessive bleeding after minor injury.

Any bleeding AE shall also be recorded with CTCAE grading.

10.12 Skin Assessments

Development of skin reactions will be monitored during the study and registered on a separate form. A dermatologist must be available for consulting at each site during the Dose Escalation part only.

Rash should be reported and graded according to the NCI-CTCAE for macular-papular skin rash according to Table 8 below:

Table 8: Grading of Skin Rash

SOC	Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin and subcutaneous tissue disorders	Rash maculo-papular	Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care activities of daily living	Life-threatening	Death

BSA = Body Surface Area; SOC=System Organ Class

In case of bulla/bullae, these should be measured and reported as AEs.

Patients should be withdrawn if they experience a study drug related grade ≥ 3 macular-papular skin rash (covering ≥ 30% of BSA), bullae (skin blisters ≥ 0.5 cm), or TEN, Steven Johnson or grade ≥ 3 cutaneous vasculitis.

10.13 Neuropathy Assessment

A standard scheme for assessment of peripheral neuropathy will be used and will be included in the eCRF to obtain information on whether potential neuropathy is peripheral or central, motor or sensory, and the localization.

10.14 Ophthalmological Evaluation

Ophthalmological evaluations should be performed at baseline and during the trial as indicated in the trial flow chart.

The ophthalmological evaluation should include collection of medical ophthalmological history (at baseline only), visual acuity assessment, Shirmer's test, slit-lamp examination, measurement of ocular pressure and funduscopic.

Patients experiencing ocular symptoms during the trial must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).

10.15 Radionuclide Bone Scan

For patients with CRPC, a radionuclide bone scan will be performed at screening, every twelve weeks during treatment, 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 four weeks prior to Visit C1-V1.

10.16 Laboratory Assessments

Blood sampling will be collected for assessment of laboratory parameters. In the Dose Escalation part, some laboratory samples will be tested at the site while others will be drawn and shipped for centralized testing. In the Cohort Expansion part, all laboratory samples will be drawn and shipped for centralized testing.

A manual with detailed description of the procedures for sampling, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels for central analysis will be provided by the central laboratory. The manual and the result reports will include all reference ranges.

Laboratory equipment in central and local laboratories may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the eCRF but must be reported to the investigator.

In case of discrepancy between central and local laboratory values, the central laboratory value will be used for study analysis purposes and the local laboratory value may be used for patient treatment decisions by the investigator (with the exception of evaluation of patient eligibility which must be supported by central laboratory data). In case of discrepancies leading to protocol deviations, this will be reported, reviewed and discussed with the sponsor medical team and documented.

If a non-serious grade ≥ 3 laboratory abnormality occurs during Cycle 1 and is assessed as related or possibly related to the study drug, then a new laboratory sample should be collected performed within 48 hours (and as close to 48 hours as possible) and reported as an unscheduled visit. This to confirm or reject the fulfillment of the DLT assessment as defined in Section 8.4.13 (Any grade ≥ 3 non-hematological AEs which occur during the first treatment cycle and are at least possibly study drug related, *excluding non-hematological laboratory abnormalities that have no clinical consequences and resolve within 48 hours*.)

A patient can always be called in for an unscheduled visit(s) if judged necessary by the investigator.

To monitor patient safety the investigator can request additional blood samples at the unscheduled visit. The reason for the visit and visit date must be recorded in the eCRF, and a sample must be provided to the central laboratory for analysis.

10.16.1 Hematology

Hematology parameters will be analyzed at the site laboratory in the Dose Escalation part and shipped for centralized analysis in the Cohort Expansion part. A blood sample will be drawn at each visit for analysis of the following parameters:

Red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count and reticulocyte count.

10.16.2 Biochemistry

Biochemistry parameters will be analyzed at the site laboratory in the Dose Escalation part and shipped for centralized analysis in the Cohort Expansion part. A blood sample will be drawn at each visit for analysis of the following parameters:

Sodium, potassium, calcium, magnesium, creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, albumin, glucose, total creatine kinase, total bilirubin, lactate dehydrogenase, uric acid, s-ferritin, C-reactive protein, and glycosylated hemoglobin.

10.16.3 Coagulation Factors

Coagulation factors will be analyzed at the site in the Dose Escalation part and shipped for centralized analysis in the Cohort Expansion part. Samples will be taken for analysis of PT, INR, aPTT, D-dimer and fibrinogen.

10.16.4 PSA and CA 125

For patients with CRPC, blood samples for PSA assessment will be drawn for local analysis in the Dose Escalation part and shipped for centralized analysis in the Cohort Expansion part.

For patients with ovarian cancer, and also for patients with endometrial cancer in the Cohort Expansion part, blood samples for CA 125 assessment will be drawn for local analysis in the Dose Escalation part and shipped for centralized analysis in the Cohort Expansion part.

10.16.5 Flow Cytometry

A blood sample will be drawn for central analysis of flow cytometry of the following:

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

Additional flow cytometry subgroups may be added based on findings going forward.

10.16.6 Pregnancy Test

A blood sample will be drawn at the Screening Visit, at C1-V1 and at the EOS Visit from all women of childbearing potential and will be analyzed at the site laboratory in the Dose Escalation part. A blood sample will be drawn at the Screening Visit; every second cycle, i.e., on Day 1 of Cycles 1, 3, 5, 7, 9, 11; at the Follow Up visits and at the EOS Visit from all women of childbearing potential and will be analyzed centrally in the Cohort Expansion part. Pregnant women may not take part in this study and will be considered as screening failures.

In order to be considered as sterilized or infertile, a patient must have undergone surgical sterilization (vasectomy/bilateral tubectomy; hysterectomy and bilateral ovariectomy) or be postmenopausal (12 months or more with no period prior to enrolment).

Safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release.

10.16.7 Immunogenicity of Tisotumab Vedotin (HuMax-TF-ADC)

Blood samples will be drawn for central analysis of ADA (both total and neutralizing). Analysis of ADA will be done in batches of several samples.

10.16.8 Hepatitis B, C, HPV and Cytomegalovirus Serology

Serology parameters will be analyzed at the site in the Dose Escalation part and centrally in the Cohort Expansion part. A blood sample will be drawn at screening for assessment of HBsAg, anti-HBs and anti-HBc, hepatitis C as well as antibodies to cytomegalovirus (CMV) antigen and serology.

For CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV polymerase chain reaction (PCR).

For hepatitis C virus (HCV), anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR.

In patients with SCCHN (Cohort Expansion part only) and cervical cancer, the HPV status must also be available at screening.

Blood samples will be drawn for assessment of antibodies to CMV antigen after the end of study drug administration (at the EOS Visit).

10.17 PK Assessments

Blood samples for assessment of tisotumab vedotin (HuMax-TF-ADC) and MMAE will be drawn for central analysis in accordance to the timing provided in Table 3 (Section 8.1.3). Two assays will be used for HuMax-TF-ADC, one detecting HuMax-TF-ADC only and one detecting HuMax-TF-ADC and non-conjugated Humax-TF.

10.18 Tumor Biopsy

A paraffin-embedded tumor tissue or cytology sample will be obtained at screening. This biopsy should be performed at least two weeks prior to dosing to ensure healing of wound.

In the Dose Escalation part an archived sample may be used as screening sample. The most recent available archived sample should be used.

In the Cohort Expansion part, tumor biopsies will be collected at screening from each patient. The most recent available archived sample can be used. If no biopsies are available, a new biopsy must be obtained before dosing. In addition, an optional tumor biopsy may be obtained three weeks (+ 2 weeks) after last dosing.

All biopsies will be analyzed retrospectively in a centralized CAP/CLIA (College of American Pathologists/Clinical Laboratory Improvement Act) certified laboratory. The IHC-assay to measure TF expression is developed on an automated staining platform and has been analytically validated for reproducibility, specificity, accuracy, range, linearity, and robustness in all eight indications evaluated in GEN701. Tumor sections will be scored for TF expression by a certified pathologist.

In addition, digital images of the stained sections will be analyzed using digital pathology software. The results will be used to correlate TF expression and clinical responses to efficacy observed in *in vivo* tumor models in rodents or tumor cell lines *in vitro*.

10.19 Exploratory Biomarkers

Plasma samples will be drawn and stored at the central laboratory for later analysis of exploratory biomarkers. The exploratory biomarkers may be tested at a non-certified laboratory if a certified laboratory is not available for performing the analysis. In this case, best efforts to ensure that the research laboratory follows the principles of GCP will be set in place.

The exploratory biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if, during or at the end of the study, it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data. Samples for biomarker evaluations will be collected as specified in the Study Flow Charts (Section 8.1.3).

10.19.1 Circulating TF

An analytically validated assay, based on detection of TF using TF-specific antibodies, is being developed to measure total levels of circulating TF in plasma. Plasma samples are collected at screening and at the first visit of Cycle 5 in the Dose Escalation part, and at screening and at Day 15 of Cycle 4 in the Cohort Expansion part, to monitor the modulation of circulating TF levels. If the analysis method has not been qualified at the end of the study, all patient samples will be destroyed.

10.19.2 Protein Biomarkers

An array of 1129 proteins is measured using the SOMAscan technology™ [redacted], US) and/or another existing platform for protein analyses. An analytical assay is available to measure all 1129 different protein levels in one plasma sample. Plasma samples are collected at screening and at the first visit of Cycle 5 in the Dose Escalation part, and at screening and at Day 15 of Cycle 4 in the Cohort Expansion part, to monitor the modulation of proteins of interest during the course of treatment.

10.19.3 Circulating cfDNA

Total cfDNA levels will be determined by quantifying so-called housekeeping genes, i.e., genes that are present in all human cells (tumor cells as well as healthy cells). The housekeeping genes to be included in this analysis are β-microglobulin, cyclophilin, GAPDH, β-actin, Alu-repeats, Ig-Kappa, Ig-Lambda, β-globin and T-cell receptor genes. This way, cfDNA analysis can be done in the same way for all patients in GEN701, irrespective of the specific type of cancer. Plasma samples are collected at screening and at shortly before dosing at Cycle 5 in the Dose Escalation part, and at screening and at Day 15 of Cycle 4 in the Cohort Expansion part, to monitor the modulation of cfDNA during the course of treatment. If the analysis method has not been qualified at the end of the study, all patient samples will be destroyed.

11. ASSESSMENT AND REPORTING OF ADVERSE EVENTS

11.1 Adverse Events Characterization

11.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Adverse events include the following:

- All suspected Adverse Drug Reactions.
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate AEs.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation.
- Any clinically significant laboratory abnormality suggesting a disease and/or organ toxicity and is of a severity that requires active management (i.e. changes of dose, discontinuation of drug, more frequent follow-up or a diagnostic investigation), unless they are associated with an already reported clinical event.

11.1.2 Definition of Serious Adverse Events

Each AE will be classified by the investigator as Serious or Non-Serious. This classification of the seriousness of the event determines the reporting procedures to be followed.

An AE that meets one or more of the following criteria/outcomes is classified as Serious:

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Medically important.
- Results in death.
- Is life-threatening.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Elective surgery, overnight for convenience or other scheduled hospitalization periods that were planned before the patient was included in this study are not to be considered serious. However, the event must be reported on the AE page in the eCRF and commented upon.

Medical and scientific judgment must be exercised in deciding whether an AE is believed to be "medically important". Medical important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

11.1.1 Definition of Infusion-Related Reaction

Infusion-related AEs are defined as any AEs occurring during infusion where the onset date and time of the event occurs within infusion time, i.e. within the following interval: infusion start date and time ≤ AE onset date and time ≤ infusion end time plus one day (24 hours) and coded by MedDRA (Medical Dictionary for Regulatory Activities) PT as "Arthralgia", "Asthenia", "Bronchospasm", "Chills", "Cough", "Hyperhidrosis", "Dizziness", "Pyrexia", "Fatigue", "Flushing", "Headache", "Hypertension", "Hypotension", "Infusion related reaction", "Lethargy", "Malaise", "Myalgia", "Nausea", "Pruritus", "Tachycardia", "Tumor pain" , or by MedDRA High Level term as "Exfoliative conditions" or "Dyspneas", "Dyspnoeas", "Breathing abnormalities" or by MedDRA High Level Group Term as "Allergic conditions". In addition, the event should be judged related to study drug by the investigator (Section 11.3.3).

11.1.2 Adverse Events of Special Interest

Based on the currently available safety profile for tisotumab vedotin (Humax-TF-ADC), the below listed events are regarded as events of special interest:

- Bleeding-related events
- Neuropathy
- Ocular events (conjunctivitis, ulceration, keratitis, symblepharon)

11.2 Adverse Event Reporting

The investigator must report all directly observed AEs and all AEs spontaneously reported by the patient. A general type of question should be used similar to "Do you have any health problems?" or "Have you had any health problems since your last visit?"

The reporting period for non-serious AEs begins from the day of first treatment administration until the EOS Visit. Any non-serious AEs (signs, symptoms and diagnosis) occurring between screening and the day of first treatment administration should be recorded as Medical History.

SAEs should be reported from the time the patient signs the ICF and until EOS or the end of the Safety Follow-up period (i.e. 30 days after last IMP dose). If the patient has died within the 30 days Safety Follow-up period after last IMP dose, this should be entered as an AE in the eCRF and reported as an SAE.

All AEs that occur in patients during the AE reporting period must be reported, whether or not the event is treatment-related.

11.2.1 Study Disease

Signs and symptoms, which according to the investigator are expected and well known consequences of the cancer type, both in intensity and frequency, should not be reported as AEs or SAEs. Any unexpected change in intensity or frequency should be reported as AE (or SAE if applicable). However, all AEs with an outcome of death (including disease progression) should be reported as an AE (in the eCRF) and as an SAE (as described in Section 11.3.6.1), from the time patients sign the ICF until 30 days after the last IMP dosing.

11.2.1.1 Pre-existing Conditions

In this study, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the medical history/physical examination form) should not be reported as an AE. If a pre-existing condition worsens during the treatment period the event should be reported as an AE.

11.2.2 Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed, should however be reported if it meets the definition of an AE. For example, an acute appendicitis should be reported as the AE and not the appendectomy.

11.3 Recording Instructions

11.3.1 Diagnosis

The diagnosis of an AE should be recorded if available. If no diagnosis is available each sign and symptom should be recorded as individual AEs.

11.3.2 Intensity

The investigator will use the NCI-CTCAE version 4.03 to describe the severity of the AE (NCI-CTCAE v4.03, 2010).

The grade assigned by the investigator should be the most severe, which occurred during the AE period.

11.3.3 Relationship to Study Drug

The investigator must assess whether or not the event is related to tisotumab vedotin (HuMax-TF-ADC). If relationship changes over time, the last judgment by the investigator should be reported. Relatedness has to be assessed and reported from the first time the AE is being reported.

11.3.4 Time of Onset

Time of onset for SAEs is the date of occurrence of the first symptom of the disease, e.g., if chest pain occurs on 01 April 2015 and the patient is hospitalized with myocardial infarction on 04 April 2015, the onset date of the SAE myocardial infarction is 01 April 2015.

11.3.5 Outcome

Outcome of the AE must be judged by investigator by the following terms:

- Recovered.
- Recovered with sequelae.
- Not recovered.
- Death.
- Unknown.

Instructions for reporting changes in an ongoing AE during a patient's participation in the study are provided in the instructions that accompany the AE eCRFs.

11.3.6 Events Requiring Immediate Reporting

11.3.6.1 Serious Adverse Events, Non-serious Grade 3 Adverse Events and Non-serious Grade 2 Ocular Adverse Events

SAEs and non-serious grade 3 AEs will be reported from the investigational site to the sponsor within 24 hours (see Sections 10.9 and 11.3.7). In addition, all non-serious grade 2 ocular AEs must be reported from the investigational site to the sponsor within 24 hours (see Section 11.3.7).

11.3.6.2 Overdose and Medication Errors

An overdose is defined as a patient receiving a dose of the study drug in excess of that specified in this protocol. All cases of overdose must be reported to the sponsor as protocol deviations within 24 hours of knowledge of the event. If the overdose results in an AE, the AE must also be recorded on the AE eCRF. If the overdose results in an SAE/non-serious grade 3 AE/non-serious grade 2 ocular AE it must be reported within 24 hours (see Section 11.3.7).

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, should be reported as protocol deviations to the sponsor within 24 hours of knowledge of the event. If a medication error results in an AE, the AE must also be recorded on the AE eCRF. Furthermore, AEs fulfilling the criteria in Section 11.3.6.1 must be reported accordingly.

Overdose, medication errors, misuse and abuse do not automatically make an AE serious, but if the consequences are serious, for example death or hospitalizations, the event is serious and must be reported as an SAE.

11.3.6.3 Pregnancy

Any pregnancy that occurs during study participation must be reported and the patient will be withdrawn from treatment immediately. To ensure patient safety, each pregnancy must be reported to sponsor or designee within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons

must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. The child must be followed to at least age one month.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to the study drug, must be promptly reported to sponsor or designee.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study patients who become pregnant while the patient is enrolled in the study. Pregnancy information must be reported to sponsor or designee as described above.

11.3.7 Reporting of Serious Adverse Events, Grade 3 Adverse Events, Grade 2 Ocular Adverse Events and Pregnancies

The required timeframes and reporting forms for reporting SAEs, non-serious grade 3 AEs and pregnancies are presented in Table 9. Please note that any ocular SAE should be reported on a SAE Report Form, any ocular non-serious grade 3 AE should be reported on a Non-serious Grade 3 Report Form, and that any ocular non-serious grade 2 AE should be reported on a Non-serious Grade 2 Ocular Adverse Event Report Form.

Table 9: Timeframes for Reporting SAEs, Grade 3 AEs, Grade 2 Ocular AEs and Pregnancies

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE Report Form	3 days 24 hours	CDS SAE DCF Site SAE DCF
Grade 3 AEs	24 hours	Non-serious Grade 3 Report Form	3 days 24 hours	CDS SAE DCF Site SAE DCF
Grade 2 ocular AEs	24 hours	Non-serious Grade 2 Ocular Adverse Event Report Form	3 days 24 hours	CDS SAE DCF Site SAE DCF
Pregnancy	24 hours	Pregnancy Form	3 days	Updated Pregnancy Form

AE=adverse event; CDS= Corporate Drug Safety; DCF=Data Clarification Form; SAE=serious adverse event

Completed SAE reports, non-serious grade 3 AE forms, non-serious grade 2 ocular AE forms or pregnancy forms must immediately be forwarded to [redacted] preferably via [redacted]. In emergency situations, a password-protected Email to [redacted] including the report can be used.

Any suspected study drug related SAE, occurring at any time after the patient has terminated study participation, should be faxed to [redacted].

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to the sponsor or designee are provided in the study procedures manual. Procedures for post-study AEs/SAEs handling are provided in the study procedures manual.

11.3.8 Suspected Unexpected Serious Adverse Reactions

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the Investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

The sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) is recorded and reported as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of seven days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the Ethics Committee according to the applicable local regulatory requirements. Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional eight days.

In EU (EMA or local competent authorities) all unexpected SAEs assessed as related to study drug by either the investigator or the sponsor will also qualify for expedited reporting. In the US (FDA) the causality assessed by the sponsor will determine whether the case requires expedited reporting.

The CRO will supply investigators with individual SUSAR reports in a form of CIOMS/MedWatch, and as biannual line listings, as required per country and local regulations.

The investigator should be aware of local reporting regulations to the IEC/IRB. The Safety CRO will either supply the investigator with the reports which should be passed on to the IEC/IRB or report directly to the IEC/IRB depending on local regulations.

11.4 Follow-Up on Adverse Events

All AEs should be followed until they are resolved or the patient's participation in the study ends, whichever comes first. Related non-serious grade ≥ 3 AEs and AEs meeting one of the serious criteria, and still ongoing after ended study participation should be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic or stable and all queries have been resolved.

11.5 Safety Communication Plan for Information to Site

In order to secure full transparency regarding patient safety-related questions to sites participating in the study, frequent communication of observations at the different sites will be required. The communication set-up will include the following components:

- SAEs, non-serious grade 3 AEs and non-serious grade 2 ocular AEs will be reported from the investigational site to the sponsor within 24 hours and medically evaluated immediately following receipt. Bi-weekly safety/medical meetings to discuss AEs and laboratory data will be held with the participation of at least the Corporate Drug Safety, Genmab Medical Officer and CRO Medical Monitor.
- Recruitment updates will be prepared by the CRO for sites and investigators including information on all SAEs, non-serious grade 3 AEs, non-serious grade 2 ocular AEs and DLTs.
- Monthly telephone conferences between all participating Investigators, CRO Medical Monitor and Genmab will be arranged. Pending severity of observed safety signals, ad hoc meetings will be held.
- A contact list with all participating investigators will be available at all sites.
- 24 hours/7 days a week availability of CRO Medical Monitor.
- Direct telephone link from investigator to Genmab Medical Officer and responsible Genmab Drug Safety Physician.
- DMC meetings following each cohort and ad hoc as needed. The outcome of the DMC meeting will be communicated to the investigators following each meeting.
- Investigators or their representative(s) will participate in the open part of the DMC meetings.

11.6 Review or Safety Boards

A DMC will be established and have its first meeting before study start (first patient screened). The DMC will include medical experts within the disease to be treated, and at least one with DMC experience. At the first meeting, the DMC will decide the future format and the degree of the information it needs in order to evaluate the patients at each dose levels.

The functions and responsibilities of the DMC will be described in the DMC Charter, which will be approved by the DMC. The DMC will receive a package of safety data, including all reported AEs and laboratory data, after each cohort has completed the first cycle of treatment. The DMC will receive a report of any SAEs and DLT immediately after review of the event by the sponsor.

Patients will be enrolled in cohorts of three patients per dose level in the Dose Escalation part. For each cohort, the DMC will evaluate aggregate safety data for the three patients in order to recommend whether it is safe to escalate to the next dose level. Before the DMC review of safety data, at least three patients in a cohort must receive one infusion and be observed for 21 days before the DMC review.

The DMC meetings will be divided into an open and a closed session. During the open sessions, representatives from the sponsor as well as one or more investigators involved in the study will participate together with the DMC members. During the closed session, only DMC members will participate.

The DMC will evaluate the data obtained at each dose level and will recommend whether the dose should be escalated as per protocol, revised to a lower level or interim level, halted

altogether or more patients are required at the same dose level to evaluate safety. In addition cumulative safety data for all cohorts will be evaluated at each DMC meeting. Available PK and/or pharmacodynamic data from the previous dose levels will be compared with known non-clinical PK, pharmacodynamic and safety information. Furthermore, any observed responses will be compared with anticipated responses. Any unanticipated responses may require a revised dose-escalation.

The conclusion of the DMC meeting will be documented in minutes and forwarded to management and relevant project members. The outcome of the DMC meeting will be communicated to the investigators. Minutes of the DMC meetings will be shared with the regulatory authorities.

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

A second safety evaluation is pre-planned when 30 patients have been dosed and followed for at least one cycle.

Further details of the constitution and procedures of the DMC meetings will be included in the DMC Charter.

12. STATISTICAL ANALYSIS

The statistical analysis of this study will be performed by [redacted].

12.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Tables, listing and figures shells will also be provided.

12.2 Analysis Populations

The full analysis population will comprise all patients who have been exposed to study drug. This population will be used for evaluation of all endpoints.

12.3 Statistical Methods

The presentations will be done separately for the Dose Escalation and the Cohort Expansion parts.

No formal statistical tests will be performed.

For efficacy analyses, 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 (CI) 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. Objective response (CR or PR) rate will be determined along with the corresponding two-sided 95% exact binomial CI.

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

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

12.3.1 Summary Statistics

All summary statistics of continuous variables will include: n, mean, median, standard deviation, minimum and maximum. 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. All CIs will be two-sided 95% CIs.

In the Dose Escalation part, individual patient profiles including information on actual dose will also be presented. Also, 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.
- By cancer type – as relevant (all dose cohorts accumulated).

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

12.4 Statistical Analysis of Primary Endpoint

Incidences of AEs, SAEs, infusion-related AEs, CTCAE grade ≥ 3 AEs, and AEs related to study drug during the study will be summarized (by system organ class and preferred term) and listed.

Also, the number of patient days (total number of days in study) will be shown for each dose group.

12.5 Statistical Analysis of Secondary Endpoints

12.5.1 Clinical Safety Data

Bleeding (major and minor), skin disorders and neuropathy will be summarized and listed separately. Abnormal findings in physical examination, body weight, ECG measurements and vital signs will be listed. Baseline visual acuity assessments in the Dose Escalation part and ophthalmological evaluation in the Cohort Expansion part will be listed.

12.5.2 Laboratory Safety Data

Laboratory assessments (Section 10.16) will be plotted and/or listed for individual patients as appropriate. Laboratory values outside normal range will be listed. Percentage change in laboratory safety parameters from baseline to subsequent visits will be derived and in listings. Special listings related to liver, kidney, heart and skin will be generated. Before and during infusion some laboratory assessments are analyzed locally for monitoring of patient safety.

12.5.3 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). In addition, maximal reductions in tumor size (as per CT-scan) will be reported separately per dose in the Dose Escalation part and per patient/indication in the Cohort Expansion part.

12.5.3.1 Definition of Response

Table 10: Definition of Response (RECIST Criteria v1.1)

	Category	Criteria
Based on target lesions	CR	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
	PR	≥ 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
	SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of LDs since the treatment started
	PD	≥ 20% increase in the sum of the LDs of target lesions, taking as reference the smallest sum of the LDs recorded since the treatment started or the appearance of one or more new lesions
Based on non-target lesions	CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
	SD	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
	PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

CR=Complete Response; LD=Longest Diameter; PD= Progressive Disease; PR=Partial Response; SD=Stable Disease

Response will be evaluated after four cycles (twelve weeks) and as best overall response. The best overall response is the best response recorded from the start of the treatment until disease progression (Table 11).

Table 11: Evaluation of Response

Target lesions	Non-target lesions	New Lesions	Response
CR	CR	No	**CR**
CR	SD or PR	No	**PR**
PR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

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 bone scan compared with a prior scan for study entry. There are no validated criteria for response on radionuclide bone scan. For control/relieve/eliminate end points, 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 six 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 too should be confirmed at the next scheduled assessment.

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 ULN and within two weeks prior to starting treatment.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

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: responders will be summarized and reported in two ways:

- Confirmed: the initial response should be confirmed by a subsequent repeat CT-scan performed no less than four weeks (± 7 days) (Section 10.7).
- All responders (i.e. confirmed and unconfirmed) will be reported.

12.5.3.2 Response Evaluation and Reporting of Results

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

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.

Individual patient data listings and summaries of objective response, best overall tumor response and disease control will be presented by dose cohort and total in the Dose Escalation part, as well as by study arm and total in the Cohort Expansion part.

Also, the maximal response (maximal change in the sum of the LD in the target lesions) in target lesions at any time on study will be reported using waterfall plots.

12.5.3.3 Progression-Free Survival

PFS is defined as the number of days from Day 1 in Cycle 1 to first PD or death. Only deaths that occurred within 60 days of the last visit will be considered in the analysis. PFS will be derived for all patients and presented graphically as well as summarized using survival analysis methods.

12.5.3.4 Duration of Response

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

12.5.3.5 Disease Control After 6, 12, 24 and 36 Weeks

Percent of patients without PD after 6, 12, 24 and 36 weeks will be summarized.

12.5.3.6 Patients with Tumor Shrinkage

Patients with tumor shrinkage (based on CT-scan evaluations) after four cycles and at end of treatment will be summarized in the Cohort Expansion part only.

12.5.4 Changes in PSA and CA 125

PSA and CA 125 will be presented graphically: individual patient plots over time and, in the Cohort Expansion part, also plots over time per patient indication (mean and median).

12.5.5 Exploratory Endpoints

Exploratory endpoints (TF expression based on biopsies, soluble TF, cfDNA and protein analyses) will be listed.

12.5.6 Host Immune Response

Titers of tisotumab vedotin (HuMax-TF-ADC) will be listed and positive/negative host immune response to HuMax-TF-ADC will be summarized (positive/negative). The association between positive/non-positive ADA and PK (pre-dose, C_{max}), major safety signals (CTCAE grade ≥ 3) and efficacy information (change in tumor size by CT-scan) will be explored.

12.5.7 Statistical Analysis of Pharmacokinetics Data

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.

The following PK parameters will be calculated based on non-compartmental methods: clearance, volume of distribution and AUC ($AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$), C_{max}, T_{max}, pre-dose

values, and half-life. The PK parameters will be calculated separately for Cycle 1 and Cycle 2.

The relation between derived PK parameters and covariates such as actual dose, weight and dose, selected laboratory parameters will be evaluated graphically.

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

Further exploratory analyses of PK data may be performed.

12.6 Handling of Missing Data or Outliers

No imputation of missing data is planned for safety endpoints and PK endpoints. If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

12.7 Subgroups and Center Effects

Subgroup analyses for the following factors are planned:

- Cancer type
- TF expression
- ADA-positivity (only for Grade ≥ 3 AEs and tumor shrinkage endpoints)

Other subgroup analyses may be performed post-hoc. Due to the low number of patients per center no investigation of center effects are planned.

12.8 Interim Analyses

An analysis of the Dose Escalation part will be performed when this part of the study is completed. A final analysis will be performed when the entire study is completed.

In addition, in the cervical and endometrial cancer indications, efficacy will be evaluated after enrolling 14 of the pre-planned 30 patients in each of these indications. After a minimum of 6 weeks of therapy, if no responder is observed among the first 14 enrolled patients, then pending DMC recommendation and approval by the sponsor's Safety committee, no further patients are to be enrolled in the relevant indication.

As part of preparations for subsequent studies, further exploratory analysis of subsets of data may be performed.

12.9 Sample Size Estimation

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

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

to six patients, are considered sufficient to establish the safety basis for escalation to the next dose level.

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

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

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

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

12.10 Clinical Study Reporting

A final report will be produced when the entire study is completed.

13. MONITORING PROCEDURES/QUALITY ASSURANCE

The sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, the sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular review of the eCRFs will be conducted in order to assess patient enrolment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The investigator must provide the monitor, sponsor representative and auditors/Inspectors with full access to all source and study documents.

13.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the patients treated under this protocol. Case histories include eCRFs and supporting data including, but not limited to, signed and dated ICFs, progress notes, hospital charts, nurse's notes, diary cards or other worksheets provided to patients, laboratory reports, ECG readings, etc.

Patient demographics and key/essential disease baseline characteristics thought to affect outcome, i.e., stratification variables and other prognostic factors, may be collected, as available, for all patients who provide written informed consent. For patients who provided informed consent and were not entered into the study, the reason the patient was not entered, i.e., did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (e.g., lost to follow-up, consent withdrawn), any AEs/SAEs and the date of ICF signature may also be collected.

13.2 Data Management

Data management in this study will be performed by [redacted].

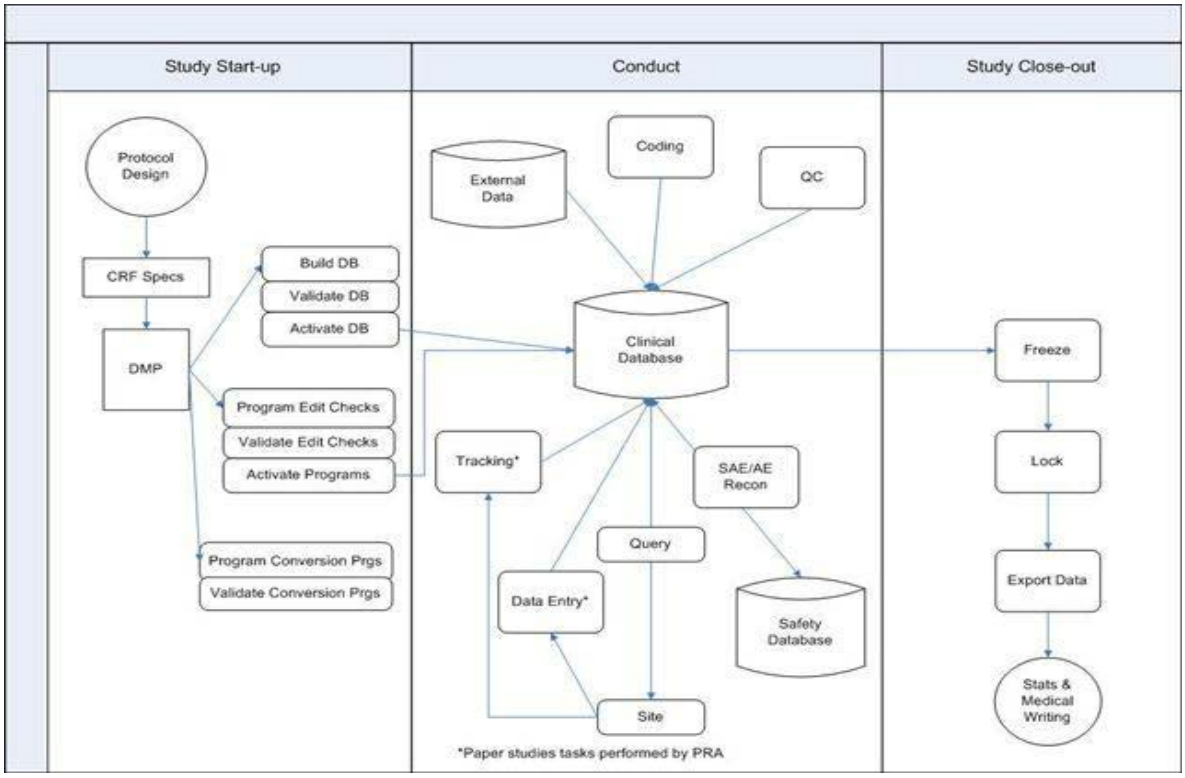
The study will be performed using electronic data capture. The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports. Any change or correction to the CRF after saving must be accompanied by a reason for the change. The investigator must review and approve, by means of an electronic signature, all data entered in the eCRF. Any corrections made after this approval will be reapproved by the investigator. The investigator should maintain a list of personnel authorized to enter data into the eCRF. Detailed data entry instructions will be provided in the eCRF Completion Guidelines.

Previous and concomitant medications will be coded using the latest available World Health Organization Drug Reference Dictionary. Medical history and AEs will be coded using MedDRA.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between Genmab and the [redacted] project team.

A Clinical Informatics Plan and Data Quality Plan will be prepared by [redacted]. The process of data collection, validation and transmission is illustrated in Figure 3.

Figure 3: [redacted] Process of Data Collection, Validation and Transmission



13.3 Study Monitoring

Sponsor or sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the electronic eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor. Further instruction will be provided in the eCRF Completion Guidelines.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that corrective action is taken to resolve any problems noted in the course of the monitoring, and that the preventive measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of the study drug to the investigator will be discontinued and study participation by that investigator will be terminated.

13.4 Inspections and Auditing Procedures

Before, during and after the study, the sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the investigator. The investigator or designee should contact the sponsor/[redacted] immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner. The investigator will forward to the sponsor a copy of any inspection records received.

14. STUDY MANAGEMENT AND MATERIALS

14.1 Data Collection

All data entered in the eCRF should be documented at the site. During each study visit, a physician participating in the study will maintain progress notes in the patient's medical records to document all significant observations. At a minimum, these notes will contain:

- That the patient has consented and are found eligible for the study (as applicable)
- The date of the visit and the corresponding day or visit in the study schedule (e.g., screening, Day 1, Day 21, etc.).
- General condition and status remarks by the patient, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the investigator's assessment as to whether or not the reported AE is study drug-related.
- Changes in concomitant medications or dosages.
- A general reference to the procedures completed.
- The signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), and other source documents will be initialed and dated on the day the change is made by the investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

Details on data validation, data transfers, origin and destination on the data, access to the transferred data, timing of the transfer and any actions that may be triggered by real-time review of those data will be documented in the Data Management Plan.

14.2 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), clinical and office charts, laboratory notes, pharmacy dispensing records, recorded data from automated instruments, photographic negatives, microfilm or magnetic media, x-rays, computer printouts, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study. There should only be one source defined at any time for any data element.

All source documents from this study will be maintained by the investigator and made available for inspection by authorized persons. The original signed informed consent for each

patient shall be filed with records kept by the investigator and a copy shall be given to the patient.

14.3 Record Maintenance

All data derived from the study will remain the property of Genmab A/S.

Records must be retained in accordance with the current ICH Guidelines E6 (R2) on GCP. All essential study documents including records of patients, source documents, eCRFs and study drug inventory must be kept on file.

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for two years after marketing application approval. If no application is filed, these records must be kept two years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The sponsor or their representative will notify the Principal Investigator of these events.

The investigator will not dispose of any records relevant to this study without written permission from the sponsor, and will provide the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor, its representatives and regulatory authorities.

If an investigator moves, withdraws from an investigation or retires the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

14.4 Confidentiality

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The investigator must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to the sponsor or the CRO, patients must not be identified. Instead, patients will only be known by initials and by the unique patient number allocated to them in order to ensure confidentiality on all study documentation. Patients will retain this unique number throughout the study. The investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for the sponsor and its representative, [redacted] personnel, the local research review board, or the US FDA to review patients' medical records as they relate to this study. Only the patient's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the sponsor.

Documents that are not for submission to the sponsor (e.g., consent forms) will be maintained by the investigator in strict confidence, except to the extent necessary to allow monitoring by the sponsor and designee, and auditing by regulatory authorities. No documents identifying patients will leave the investigative site and patient identity will remain confidential in all publications related to the study.

15. ADMINISTRATION PROCEDURES

15.1 Regulatory Approval

Genmab A/S or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No patient may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the investigator and to the IEC(s)/IRB(s).

15.2 Protocol Amendments

In accordance with ICH Topic E 6 (R2) Guideline for GCP the investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and documented approval from the IEC/IRB of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IEC/IRB assuming this responsibility. The investigator must await IEC/IRB approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to patients. In these cases, the IEC/IRB must be notified within five days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IEC/IRB, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IEC/IRB, the investigator and/or sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the patient, the currently approved written ICF will require modification. The modified ICF must also be reviewed and approved by the sponsor, appropriate regulatory authorities, and the IEC/IRB. In such cases, repeat informed consent must be obtained from patients enrolled in the study before participation continues.

15.3 Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the patient requires immediate intervention based on the judgment of the investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the investigator or designee must contact the Medical Monitor at the earliest possible time by

telephone. This allows for an early joint decision to be made as to whether or not the patient should continue in the study. The investigator, the sponsor, and the Medical Monitor will document this decision. In addition, a potential serious breach must be reported to the competent authorities immediately.

15.4 Publication Policy

The sponsor acknowledges the investigator's right to publish the entire results of the study, regardless of the outcome, in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors (http://www.icmje.org/urm_full.pdf, updated April 2010).

The international coordinating investigator will, together with the sponsor, decide on the publication strategy and has the right to publish and present the results and methods as first author of multicenter publications. Co-authorship will be decided by the sponsor and the international coordinating investigator and will be limited to a number of persons who have contributed substantially in the design, analysis and conduct of the study or the writing and presentation of results. The sponsor will have representation in the list of authors.

Publications are subject to the following conditions:

- No publication before the completion of the study at all participating sites without written agreement with the sponsor.
- All proposed publications and presentations, including any modifications or amendments, shall be submitted to the sponsor for its review at least 30 days before such presentation or publication is submitted to any third party.
- Publications shall not disclose any sponsor confidential information and property (not including the study results, which can be published as described elsewhere in this section).

15.5 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

15.6 Insurance, Indemnity and Compensation

Genmab A/S undertakes to maintain an appropriate clinical study insurance policy.

Deviations from the study protocol - especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods - are not permitted and shall not be covered by the statutory patient insurance scheme.

15.7 Discontinuation of the Study

This study may be terminated by the sponsor. The study may also be terminated prematurely at any time when agreed to by both the investigators and the sponsor as being in the best interests of patients, and justified on either medical or ethical grounds. In terminating the study, Genmab A/S, [redacted] and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

15.8 Study Center File Management

The investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

(1) Investigator's Brochure;

(2) Current, signed version of the protocol and any previous versions of the protocol;

(3) Protocol amendments (if applicable);

(4) Operations Manual (if applicable);

(5) Current ICF (blank) and any previous versions of the ICF;

(6) Curricula Vitae of investigator(s) and sub-investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;

(7) Documentation of CA/IEC/IRB approval of the protocol, the ICF, any protocol amendments, and any ICF revisions;

(8) All correspondence between the investigator, IEC/IRB, and the sponsor/designee relating to study conduct;

(9) Laboratory certification(s);

(10) Patient management logs (screening log, etc.);

(11) Monitoring log;

(12) Study drug invoices;

(13) Delegation log;

(14) Source document location list.

16. REFERENCE LIST

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17. APPENDICES

17.1 Appendix 1: ECOG Performance Status Scale

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

** As published in Am. J. Clin. Oncol.:*
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-55, 1982.

17.2 Appendix 2: Highly Effective Methods of Contraception

For countries where two highly effective methods of contraception are required, the following definitions are provided (ICH M3).

Highly effective method of contraception / birth control as defined in ICH (M3)

Methods of birth control which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.

Barrier Contraceptive

A contraceptive device that physically prevents sperm from entering the endometrial cavity and fallopian tubes (e.g. male condom, female condom or diaphragm).

Acceptable forms of effective contraception include:

1. Established use of oral, injected or implanted hormonal methods of contraception. *(Safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release.) [The decision to allow use of hormonal contraceptives should be based on the Investigational Medicinal Product's metabolism and potential for interactions, pharmacology and the adverse event profile (e.g. vomiting)]*.
2. Placement of an intrauterine device or intrauterine system. *[Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g. steel or copper wire]*
3. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. *[The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:*
    - *Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.*
    - *However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled.* ***Therefore, spermicides are not a barrier method of contraception and should not be used alone****.]*
4. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). *[For female subjects on the study, the vasectomized male partner should be the sole partner for that subject]*.
5. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*.

Two forms of highly effective contraception

For certain studies, e.g. in the event of teratogenicity or lack of adequate reproductive toxicity data, there is a requirement for two forms of highly effective contraception. In this situation, subjects should be instructed to use two different forms of effective contraception (e.g. from the list above).

17.3 Appendix 3: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and

therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should

include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations

the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.