STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNTV-002
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Protocol Title:	Open Label Phase 2 Study of Tisotumab Vedotin for Patients with Platinum-Resistant Ovarian Cancer with a Safety Run-in of a Dose-Dense Regimen
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APPROVAL SIGNATURES

Product:	Tisotumab Vedotin
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The individuals signing below have reviewed and approve this statistical analysis plan.

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LIST OF ABBREVIATIONS

3Q4W	three times every 4 weeks
AE	adverse event
AESI	adverse events of special interest
ATA	antitherapeutic antibodies
CA-125	Cancer antigen 125
CI	confidence interval
CPI	checkpoint inhibitor
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy-evaluable
EOS	end of study
EOT	end of treatment
FAS	full analysis set
GCIG	Gynecologic Cancer Intergroup
IV	intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Affairs
MMAE	monomethyl auristatin E
NCA	noncompartmental analysis
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient reported outcomes
PROC	platinum-resistant ovarian cancer
PROMIS	Patient-Reported Outcomes Measurement Information System
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SAE	serious adverse event
SD	stable disease
SMC	Safety Monitoring Committee
TAb	total antibody
TEAE	treatment-emergent adverse event

TF	Tissue Factor
TTR	time to response
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNTV-002, entitled "Open Label Phase 2 Study of Tisotumab Vedotin for Patients with Platinum-Resistant Ovarian Cancer with a Safety Run-in of a Dose-Dense Regimen", Original dated 20July2018. Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final CSR. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the CSR.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- (Safety run-in) Evaluate safety and tolerability of a dose-dense regimen of tisotumab vedotin
- (Parts A and B) Evaluate antitumor activity of tisotumab vedotin

2.2 Secondary Objectives (Parts A and B)

- Evaluate the safety and tolerability of tisotumab vedotin
- Evaluate preliminary antitumor activity of tisotumab vedotin
- Evaluate durability of response in patients who respond to tisotumab vedotin
- Evaluate stability and control of disease
- Evaluate the timing of responses
- Evaluate progression-free survival (PFS) of patients treated with tisotumab vedotin
- Evaluate overall survival of patients treated with tisotumab vedotin
- Assess pharmacokinetics (PK) of tisotumab vedotin
- Assess immunogenicity of tisotumab vedotin

2.3 Additional Objectives (Parts A and B)

- Evaluate Tissue Factor (TF) expression-response relationship
- Assess biomarkers of biological activity and resistance and predictive biomarkers of response
- Patient-reported outcomes (Parts A and B, US patients only)

3 STUDY ENDPOINTS

3.1 Primary Endpoint

For the safety run-in, the primary endpoint is the incidence of dose limiting toxicities (DLTs) or other unacceptable toxicities. For Parts A and B, the primary endpoint is confirmed objective response rate (ORR) (confirmed complete response [CR] and confirmed partial response [PR] per RECIST v1.1) as determined by the investigator.

3.2 Secondary Endpoints (Parts A and B)

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Investigator-determined confirmed and unconfirmed ORR as measured by RECIST v1.1 (all responses)
- CA-125 response rate
- Combined RECIST/CA-125 overall response
- Investigator-determined duration of response (DOR) as measured by RECIST v1.1
- Investigator-determined disease control rate (DCR) as measured by RECIST v1.1
- Investigator-determined time to response (TTR) as measured by RECIST v1.1
- Investigator-determined PFS as measured by RECIST v1.1
- Overall survival (OS)
- Selected PK parameters for tisotumab vedotin and monomethyl auristatin E (MMAE)
- Incidence of anti-therapeutic antibodies (ATAs) to tisotumab vedotin

3.3 Additional Endpoints (Parts A and B)

- TF expression-response relationship following treatment with tisotumab vedotin
- Relationship between biomarkers in blood and tumor tissue to efficacy, safety, or other biomarker endpoints following treatment with tisotumab vedotin
- PROMIS and an NCI PRO-CTCAE questionnaire customized to focus on ocular symptoms, bleeding, and gastrointestinal symptoms, as well as other questions added by the sponsor

4 STUDY DESIGN

This is an open-label, phase 2 study with an initial safety run-in period. The safety run-in period will evaluate the safety of a dose-dense schedule and will start at a 0.9 mg/kg dose level. If 0.9 mg/kg is considered safe and tolerable, the dose level will be escalated to 1.2 mg/kg. Otherwise it will be de-escalated to 0.65 mg/kg. Each dose level will enroll approximately 6 patients. Patients who do not complete the DLT period will be replaced.

A dose level is considered safe and tolerable if no more than 1 patient experiences a DLT among 6 patients during the DLT period. The highest dose level that is considered safe will be the recommended phase 2 dose (RP2D) and will be used in Part A. If no RP2D for the dose-dense schedule is identified, Part A will be a single arm of the Q3W regimen and Part B will not enroll.

In Part A, 60 patients will be randomized in a 1:1 ratio to receive tisotumab vedotin 2.0 mg/kg intravenously (IV) every 3 weeks (Q3W regimen) or the safety run-in RP2D on Days 1, 8, and 15 of every 4-week cycle (dose-dense regimen; 3Q4W) if a RP2D has been identified. Randomization will be stratified by first line vs. second line PROC and histology (serous vs. non-serous).

Based upon antitumor activity and safety data, one Part A treatment arm may be expanded to enroll up to an additional 70 patients to further characterize safety and antitumor activity of tisotumab vedotin for patients with PROC. The analysis to support expansion will be conducted when approximately 30 patients per arm have at least one post-baseline response assessment per RECIST v1.1 or have discontinued from the study or started subsequent cancer therapy.

Part B will enroll approximately 80 patients with PROC including approximately 60 patients who have received 1 to 3 prior lines of therapy, including bevacizumab treatment. Part B will further characterize the long-term efficacy, safety, and PK assessments of 0.9 mg/kg tisotumab vedotin on Days 1, 8, and 15 of every 4-week cycle (dose-dense regimen) if the 0.9 mg/kg dose level is considered safe and tolerable in the safety run-in period. Enrollment in this cohort may discontinue when Part A begins enrollment.

Interim futility analysis will be performed on Part B after at least 20 patients with 1 to 3 prior lines of therapy, including bevacizumab treatment, have been treated and had at least one response assessment post-baseline. The Bayesian predictive probability approach will be used to assess the futility criteria. Based on activity and safety data, together with the predictive probability of success (PPoS), a cohort may be stopped early by the sponsor. A cohort may also be discontinued at any point at the discretion of the sponsor.

5 ANALYSIS SETS

5.1 Full Analysis Set (FAS)

The full analysis set (FAS) includes all patients who received any amount of study drug. All efficacy analyses will be based on the FAS.

5.2 Safety Analysis Set

The safety analysis set includes all patients who received any amount of study drug, and thus is equivalent to the FAS. All safety analyses will be based on the safety analysis set.

5.3 PK Analysis Set

PK analysis set includes enrolled patients who received any amount of study drug and at least one PK parameter can be estimated. The PK parameters will be tabulated using the PK analysis set.

5.4 Anti-therapeutic Antibody (ATA) Evaluable Set

ATA evaluable set includes patients who had a baseline ATA status and at least one ATA sample evaluated at post treatment. ATA analyses will be based on the ATA evaluable set.

5.5 Efficacy-Evaluable (EE) Analysis Set

The efficacy-evaluable (EE) analysis set includes patients who received any amount of study drug and had at least one post-baseline disease assessment per RECIST v1.1 or had clinical progression per investigator judgement. The EE analysis set will be used for supplemental analysis of the objective response rate and the disease control rate.

5.6 CA-125 Evaluable Analysis Set

The CA-125 evaluable analysis set includes patients who have an elevated baseline CA-125 value of ≥2 x ULN (upper limit of normal) within 2 weeks prior to the first dose of study drug. The CA-125 evaluable analysis set will be used for the analysis of CA-125 response rate.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

Patients enrolled in the safety run-in portion and Part A and Part B portion of the study will be summarized separately. All analyses in the Part A and Part B portion will be presented by cohort and for patients with 1 to 3 lines of prior therapy, including bevacizumab treatment unless otherwise specified. Descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages per category for categorical variables.

Unless otherwise specified, confidence intervals (CI) will be calculated at 2-sided 95% level.

The 2-sided 95% exact CI using the Clopper-Pearson method will be calculated for the response rates where applicable (e.g., ORR) (Clopper 1934).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to Section 16 of the CSR.

All statistical Tables, Listings and Figures will be produced using SAS®, version 9.3 or higher. Other statistical software, if used, will be described in the CSR.

6.2 Determination of Sample Size

Up to approximately 222 patients may be enrolled in the study. This includes approximately 6–12 patients in the safety run-in phase, approximately 30 patients in each of 2 randomized Part A cohorts, and the possible expansion of an additional 70 patients in one of the 2 Part A cohorts. Part B will enroll approximately 80 patients including approximately 60 patients who have received 1 to 3 prior lines of therapy, including bevacizumab treatment.

Analysis regarding expansion of Part A will be conducted when approximately 30 patients per cohort have at least one post-baseline response assessment per RECIST v1.1 or have discontinued from the study or started subsequent cancer therapy.

A cohort may be expanded to further characterize antitumor activity if the safety profile is acceptable, other efficacy endpoints are comparable to current standard of care, and the number of confirmed CR or PR meet cohort-specific criteria.

The sample size is not based on power calculations for formal hypothesis testing, but is selected based on ORR estimate precision as characterized by 95% confidence intervals (CIs). For a sample size of 30 patients (Part A) and 60 patients (Part B with 1 to 3 prior lines of therapy, including bevacizumab treatment) per cohort (or 100 patients, if a treatment arm from Part A is expanded), assuming the confirmed ORR is between 20% and 40%, the 2 -sided 95% exact CIs are summarized below.

Confirmed ORR	95% Exact CI (N=30)	95% Exact CI (N=60)	95% Exact CI (N=100)
15%	(4%, 31%)	(7%, 27%)	(9%, 24%)
20%	(8%, 39%)	(11%, 32%)	(13%, 29%)
30%	(15%, 49%)	(19%, 43%)	(21%, 40%)
40%	(23%, 59%)	(28%, 53%)	(30%, 50%)

6.3 Randomization and Blinding

This is an open-label phase 2 study with an initial safety run-in phase. The safety run-in will evaluate the tolerability of dose-dense regimen. If the tolerability is confirmed, the study will proceed to Part A and Part B. In Part A, randomization will be stratified by first line vs. second line PROC and histology (serous vs. non-serous). Patients will be randomized in a 1:1 ratio to receive tisotumab vedotin 2.0 mg/kg Q3W or the RP2D dose-dense regimen.

Randomization is used in this study to minimize bias and not as a basis for statistical inference as the study includes no formal statistical hypothesis testing.

If the tolerability of dose-dense regimen is not confirmed after the safety run-in, Part A will be a single-arm treated with the Q3W dosing schedule and Part B will not enroll.

Part B will be a single arm of the 0.9 mg/kg dose-dense regimen.

6.4 Data Transformations and Derivations

6.4.1 General

Reported age in years will be used; if not available, age at informed consent in years will be calculated with the SAS® INTCK function (with method specified as "continuous") using informed consent date and birth date.

Time variables based on two dates (e.g., Start Date and End Date) will be calculated as (End Date – Start Date +1 [in days]) unless otherwise specified in the planned analysis section.

Specifically, Study Day will be calculated as (Date–First Dose Date+1) for dates on or after the first dose date. The date of first dose will be Study Day 1. For dates prior to the first dose date, Study Day will be calculated as (Date–First Dose Date). For example, the date before the first dose date will be Study Day -1.

The following unit conversion will be implemented unless otherwise specified:

Months=Days/30.4375

Years=Days/365.25

Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

The end-of-treatment (EOT) date will be the date when the EOT visit is performed; if an EOT visit is not performed then the EOT date will be either the end-of-study (EOS) date or 30 days after the last dose of any study drug, whichever is earlier.

6.4.2 Best Response

The determination of antitumor activity will be based on objective response assessments made by the investigator according to the RECIST v1.1 (Eisenhauer 2009). Only response assessments on or prior to the start date of any new anticancer therapy will be considered for best response. The patient's best confirmed response will be the best demonstrated response to date that has been confirmed, when confirmation is required (i.e. for PR and CR only). When confirmation is not required, the patient's best response will be the best demonstrated response to date. The patient's best response will be used in determining the ORR.

A response (CR or PR) will be considered confirmed if the subsequent disease assessment conducted no earlier than 4 weeks after the initial response still shows CR or PR (i.e., CR followed by CR or PR followed by PR or CR). A patient will have a best response of SD if there is at least one SD assessment (or better) ≥5 weeks after the start of treatment and the patient does not qualify for confirmed CR or PR. RECIST v1.1 outlines scenarios for best overall responses when confirmation of CR and PR is required.

In addition to radiographic tumor assessments, expression level of CA-125 will also be monitored to assess CA-125 response according to the GCIG criteria.

6.4.3 Response Assessment Dates

For efficacy assessments, the date of response assessment of CR, PR, or SD will be the latest of all radiologic scan dates for the given response assessment. The date of progression per RECIST v1.1 will be the earliest of all radiologic scan dates that PD response has been documented, i.e., the earliest of

- Date(s) of target lesion assessments with target lesion response of PD
- Date(s) of non-target lesion assessments with lesion status of unequivocal progression
- Date(s) of documenting new unequivocal lesion(s)

6.5 Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified. Missing AE start date and/or end date will be imputed while calculating duration of events and treatment-emergent status (see Appendix A for imputation details).

For time-to-event endpoints, e.g., DOR, PFS, and OS, patients who have no specific event will be censored as specified for each respective endpoint in Section 7.5.

Patients who do not have at least 2 post-baseline response assessments (initial response and confirmation scan) will be counted as non-responders for analysis of the primary endpoint.

Missing subsequent anticancer treatment start date will be imputed while deriving the time-to-event endpoints as applicable (see Appendix B for imputation details).

For prior therapies end dates, if month and year are present and only day is missing, day may be imputed. The end day will be imputed with the last day of the month or 21 days before the first dose of study drug, whichever is earlier. If the imputed end date is earlier than start dates, the end day will be imputed with the day after the start date. If month or year is missing, no imputation will be performed.

For prior therapies start dates, if month and year are present and only day is missing, day may be imputed. The imputed day will be the first day of the month. If month or year is missing, no imputation will be performed.

Unless otherwise specified, if the numeric value of a clinical laboratory test is not available because it is below the lower limit of quantification (LLOQ), "< LLOQ" should be used whenever applicable. In cases where a numeric value is required, e.g., calculating the mean and standard deviation, the LLOQ/2 will be used for the calculation.

6.6 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned in this study.

6.8 Examination of Subgroups

Subgroups would be conducted for the primary endpoint (confirmed objective response rate) and other key secondary efficacy endpoints if appropriate. Subgroups may include but are not limited to the following:

- Age (18–64, ≥65 years old)
- Platinum-free interval (<3 vs 3-6 month)
- First line vs. second line PROC
- TF expression (less than or equal to median, above median)
- Prior treatment with CPIs (yes, no)
- Prior treatment with PARP inhibitors (yes, no)
- ECOG performance score at baseline (0, 1)
- Number of prior systemic therapies (including in the PROC setting) (1, 2, 3, ≥4)

Platinum-free interval is defined as the time from the end of the latest platinum-based therapy to the earlier of disease progression from the latest platinum-based therapy or the start of the first line systemic therapy in the PROC setting.

If the number of patients in some subgroups is not sufficiently large (e.g., <10% of the total sample size), the subgroup analysis may not be performed or the subgroups may be combined if applicable.

6.9 Covariates

No adjustments for covariates are planned in the analyses.

6.10 Timing of Analyses

The primary analysis of study will be conducted when all treated patients have had an opportunity to be followed for at least 6 months. Subsequent data cutoff dates may be defined to assess longer term clinical benefit with further follow up.

A safety analysis will be conducted at end of DLT period for each dose level in the safety run-in portion to evaluate the tolerability of dose-dense regimen.

7 PLANNED ANALYSES

7.1 Disposition

Patient disposition will be summarized by cohort and total for patients in FAS with descriptive statistics. Patients who discontinue study treatment and patients who withdraw from the study will be summarized along with reason for discontinuation or withdrawal. The

number of patients who signed the informed consent and the number and percentage of patients in each analysis set will be summarized. The reasons for screen failure will also be summarized, if applicable.

The number of patients enrolled at each site will be summarized.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age at consent, gender, ethnicity, race, baseline height, weight, and ECOG score will be listed and summarized by cohort and total using the FAS. Disease specific characteristics will be listed and summarized by cohort and total using the FAS. Disease characteristics may include cancer stage at diagnosis, previous cancer-related treatments, number of prior systemic therapies, number of prior cytotoxic chemotherapy in the PROC setting, platinum-free interval, histology, genetic markers, and tissue factor expression.

7.3 Protocol Deviations

Important protocol deviations (defined as protocol violations by Seagen, Inc.) are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the patient's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be summarized by category. A list of patients with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized with descriptive statistics by cohort using the safety analysis set. Summaries may include but are not limited to the following:

- Duration of treatment (in weeks), for the Q3W cohort, which is defined as time from the first study dose to the earliest of Day 21 of the last treatment cycle, EOT visit, death date, or start date of subsequent anticancer therapy if applicable. For the dose-dense cohort, duration of treatment is defined as time from the first study dose to the earliest of Day 28 of the last treatment cycle, EOT visit, death date, or start date of subsequent anticancer therapy if applicable
- Number of cycles per patient
- Number and percentage of patients by number of treated cycles
- Cumulative dose received (in mg), which is defined as sum of the actual dose across all cycles.
- Average dose per week
- Relative dose intensity (RDI), which is defined as the absolute dose intensity (ADI) divided by the intended dose intensity (IDI). That is, RDI = ADI/IDI × 100, where ADI is defined as the actual dose in mg/kg per week and IDI is defined as the intended dose in mg/kg per week regardless of dose reduction in later cycles. For

Q3W cohort IDI is 2/3= 0.667 mg/kg/wk. For dose-dense cohort IDI is 0.9*3/4=0.675 mg/kg/wk if dose level is 0.9 mg/kg or 0.65*3/4=0.488 mg/kg/wk if 0.65 mg/kg.

- Number and percentage of patients whose dose was ever modified, which will be summarized by modification type (delay, reduction, elimination, unplanned dose adjustment). The number and percentage of doses that were modified may also be summarized.

7.5 Efficacy Analyses

All efficacy analyses will be descriptive in nature and all efficacy endpoints will be analyzed by cohort and total using the FAS unless otherwise specified. In addition, the ORR and DCR will also be analyzed using the EE set.

7.5.1 Primary Endpoint

7.5.1.1 Confirmed Objective Response Rate (ORR)

The primary efficacy endpoint of this study is the confirmed ORR per investigator assessment. The confirmed ORR is defined as the proportion of patients who achieve a confirmed CR or PR according to RECIST v1.1 (Eisenhauer 2009). Patients who do not have at least 2 post-baseline response assessments (initial response and confirmation scan) will be counted as non-responders. Confirmation means a PR is followed by a PR or CR at least 4 weeks later, or a CR is followed by a second CR at least 4 weeks later.

The confirmed ORR of each cohort and its exact 2-sided 95% CI will be calculated.

This endpoint will also be summarized by the subgroups defined in Section 6.8.

7.5.2 Secondary Endpoints

7.5.2.1 Confirmed and Unconfirmed ORR

Confirmed and unconfirmed ORR is defined as the proportion of patients who achieve a CR or PR according to RECIST v1.1 as assessed by the investigator. These include patients with confirmed responses as well as those whose responses were not confirmed or had not yet been assessed for confirmation. Patients who do not have at least 1 post-baseline response assessment will be counted as non-responders.

The confirmed and unconfirmed ORR will be estimated for each cohort and its exact 2-sided 95% CIs will be calculated.

7.5.2.2 CA-125 Response Rate

Baseline CA-125 is the most recent non-missing measurement no more than 14 days prior to the first dose of study drug.

CA-125 response rate is defined as the proportion of patients who have at least a 50% reduction in CA-125 value from baseline. The response must be confirmed in a subsequent sample collected ≥28 days after the prior sample. The value of the confirmatory sample must

be ≤110% of the prior sample. The CA-125 evaluable analysis set will be used for the analysis of CA-125 response rate.

In addition, summary statistics of CA-125 values and changes from baseline will be tabulated by scheduled visit using the FAS.

7.5.2.3 Combined RECIST/CA-125 Overall Response

The combined RECIST/CA-125 overall response is defined as the proportion of patients whose best response is a CR or PR according to the Gynecological Cancer Intergroup (GCIG) combined RECIST and CA-125 criteria (Rustin 2011). For those who are not in the CA-125 evaluable analysis set, patients will be assessed to determine whether they have PD or not according to GCIG CA-125 criteria. Then the combined overall response will be assessed as indicated in Table 7.

Table 1: Overall response by RECIST and CA-125 criteria

RECIST Response	CA-125 Response	Combined RECIST/CA-125 Response
CR	Response and normalized[a]	CR
CR	Response	PR
CR	Not response and not PD[b]	PR
PR	Response	PR
PR	Not response and not PD[b]	PR
SD	Response	PR
SD	Not response and not PD[b]	SD
NE[c]	Response	PR
PD >28 days from CA-125 response	Response	PR
PD ≤28 days from CA-125 response	Response	PD
PD	Not response and not PD[b]	PD
Any	PD[b]	PD

a Normalized means CA-125 value within the reference range

b Progression of CA-125 levels is defined as: 1) CA-125 ≥2x ULN on 2 occasions at least 1 week apart for patients with elevated CA-125 before treatment and later normalizes, 2) CA-125 ≥2x nadir value on 2 occasions at least 1 week apart for patients with elevated CA-125 before treatment which never normalizes, or 3) CA-125 ≥2x ULN on 2 occasions at least 1 week apart for patients with CA-125 in the reference range before treatment.

c Target lesions are not all evaluated, non-target lesions are non-PD, and no new lesions appear.

7.5.2.4 Disease Control Rate

DCR is defined as the proportion of patients who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator, or meet the SD criteria at least once after start of study treatment at a minimum interval of 12 weeks (-1 week window). Patients who do not have at least 1 post-baseline response assessment or patients whose response cannot be assessed will be counted as not achieving disease control.

As an exploratory analysis, DCR will also be calculated without requiring confirmation of CR or PR for disease control.

DCR will be estimated for each cohort and its exact 2-sided 95% CIs will be calculated.

7.5.2.5 Duration of Response

DOR is defined as the time from the first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD or death due to any cause, whichever comes first.

DOR data will be censored as described below:

- Patients who do not have PD and are still on study at the time of an analysis will be censored at the date of last disease assessment documenting absence of PD.
- Patients who have started a new anticancer treatment prior to documentation of PD will be censored at the date of last disease assessment prior to the start of new treatment.
- Patients who are removed from the study prior to documentation of PD will be censored at the date of last disease assessment documenting absence of PD.
- Patients who have death or PD after two or more consecutive missed/NE tumor assessments will be censored at the date of the last adequate tumor assessment prior to the missed visits.

DOR will only be calculated for patients who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator.

DOR will be analyzed by cohort using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median DOR and its 2-sided 95% CI will be calculated as appropriate.

Sensitivity analyses may be performed for DOR to evaluate the robustness of treatment effects:

- A sensitivity analysis may be performed by considering death or PD per RECIST v1.1 as an event regardless of missing disease assessments.
- A second sensitivity analysis may be performed for DOR to evaluate the robustness of results by including investigator claim of clinical progression as an event. Patients who are not evaluable or have a response of SD or better per RECIST v1.1 at the same visit as investigator claim of clinical progression will be counted as disease progression (i.e., an event). The date of progression will be the date of investigator claim of clinical progression or PD date per RECIST v1.1, whichever is earlier.

7.5.2.6 Time to Response

TTR is defined as the time from the start of study treatment to the first documentation of objective response (CR or PR that is subsequently confirmed).

Patients who do not achieve objective response will have the TTR censored as described below:

- Patients with a PFS event (i.e., disease progression or death due to any cause) or who start a new anticancer treatment will be censored at the trial-maximum follow-up time (i.e., last patient last visit – first patient first visit + 1).
- All other patients will be censored at the date of last disease assessment.

TTR will be analyzed by cohort using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median TTR and its 2-sided 95% CI will be calculated as appropriate.

In addition, TTR will be summarized for patients who achieve a confirmed CR or PR.

7.5.2.7 Progression-Free Survival (PFS)

PFS is defined as the time from the start of study treatment to the first documentation of PD or death due to any cause, whichever comes first.

The same censoring rules as outlined in Section 7.5.2.5 for DOR will be applied to PFS. Patients who are known to have died and do not have an evaluation of tumor response after their first dose of study drug will be censored at Day 1.

PFS will be analyzed by cohort using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its 2-sided 95% CI will be calculated as appropriate. The PFS rates at 3 and 6 months, and every 3 months thereafter, will be reported and their 2-sided 95% CIs will be calculated.

Sensitivity analysis of PFS will be performed as described in Section 7.5.2.5 for DOR.

7.5.2.8 Overall Survival (OS)

OS is defined as the time from the start of study treatment to date of death due to any cause. In the absence of death, survival time will be censored at the last date the patient is known to be alive (i.e., date of last contact). Patients lacking data after their first dose of study drug will have their survival time censored at Day 1.

OS will be analyzed by cohort using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its 2-sided 95% CI will be calculated as appropriate. The OS rates at 6 and 12 months, and every 6 months thereafter, will be reported and their 2-sided 95% CIs will be calculated.

7.6 Safety Analyses

All safety analyses will be performed by cohort and total using the safety analysis set.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 5.0 or higher).

Concomitant medications will be coded using WHO Drug (version: June 2016 or more recent).

7.6.1 Adverse Events

AEs will be summarized by MedDRA preferred term in descending frequency of occurrence unless otherwise specified. For incidence reporting, if a patient reports more than one AE that was coded to the same system organ class or preferred term, the patient will be counted only once for that specific system organ class or preferred term.

Treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment and with onset date on or before 30 days after the last dose of study drug. See Appendix B for details regarding treatment-emergent classification.

Summaries of AEs will be provided by cohort and total for the following:

- TEAEs
- Grade 3 or higher TEAEs
- DLTs
- TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term, and maximum severity. At each system organ class or preferred term, multiple occurrences of events within a patient are counted only once at the highest severity
- TEAEs related to tisotumab vedotin
- TEAEs leading to dose delay
- TEAEs leading to dose reduction
- TEAEs leading to dose elimination
- TEAEs leading to unplanned dose adjustment
- TEAEs leading to treatment discontinuation
- TEAEs leading to death
- Infusion related reactions

- Treatment-emergent SAEs
- Treatment-emergent SAEs by system organ class and preferred term
- Treatment-emergent SAEs related to tisotumab vedotin
- Treatment-emergent Adverse Events of Special Interest (AESI) by system organ class, preferred term and maximum severity
- Treatment-emergent AESI
- Serious AESI

All TEAEs, Treatment-emergent SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to death, and DLTs will be listed.

7.6.1.1 Adverse Events of Special Interest

Adverse events of ocular AEs, peripheral neuropathy, and bleeding are considered AESI. The search criteria for AESI will be maintained in a separate document and will be finalized prior to database lock. Shift tables comparing the highest post-baseline to baseline CTCAE grade will be presented when applicable.

Time to onset will be summarized for subjects who have the events that meet certain search criteria. Time to onset is defined as time (days) from the date of first dose to the start date of first event (start date of first event – date of first dose + 1).

Time to resolution will be summarized for events that meet certain search criteria and have the outcome of 'recovered/resolved' or 'recovered/resolved with sequelae'. Time to resolution is defined as time (days) from the start date of the event to the end date of the same event (end date of the event – start date of the event + 1).

For events that are not resolved, improvement is defined as a decrease by at least one grade from the worst grade as of the latest assessment. For events that meet the definition of 'improvement', time to improvement will be calculated as time from the worst grade of the event to the date the event is improved.

Time to onset, resolution and improvement will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Time to onset will be summarized at the subject level. Time to resolution and improvement will be summarized at the event level.

7.6.1.2 Ophthalmological Exam and Eye Examination Data

The data for ophthalmological exam and eye examination at baseline and other applicable visits will be listed. Summary statistics of ophthalmological exam and eye examination results will be tabulated by visit where appropriate. Shift tables comparing the worst post-baseline to baseline results will be presented. Summaries may include but are not limited to

visual acuity, Schirmer's test, slit lamp test, conjunctivas and corneas including staining, intraocular pressure, and fundoscopy.

7.6.2 Clinical Laboratory Parameters

All laboratory results up to the end of treatment visit will be presented in standardized units. Grading of laboratory values will be assigned programmatically per the NCI CTCAE. Summary statistics of selected laboratory results (complete blood count with differential, serum chemistry, and coagulation panel) and changes from baseline will be tabulated by scheduled visit. The highest post-baseline grade will be presented for each lab test. Shift tables comparing the highest post-baseline to baseline CTCAE grade will be presented based on number of subjects in safety analysis set with a baseline and at least one post-baseline laboratory value.

In addition, clinical laboratory data may be presented graphically for selected lab tests, by scheduled visit.

Laboratory values will be listed with grade per CTCAE and flagged when values are outside the normal reference range.

7.6.3 Deaths

The number of total deaths, deaths that occur within 30 days of last study treatment, and deaths that occur more than 30 days after last study treatment as well as the relationship to disease will be summarized. In addition, cause of death will be displayed in MedDRA preferred term (unless otherwise specified) and summarized. Death information will be listed by patient.

7.6.4 Concomitant Medications

Concomitant medications will be summarized by the World Health Organization (WHO) drug substance name. The number and percentage of patients taking concomitant medications will be tabulated for the following, but not limited to:

- Ocular premedication and preventive eye therapy which include ocular vasoconstrictor eye drops, eye cooling pads, steroid eye drops, and lubricating eye drops
- Anti-coagulation therapy if applicable
- Granulocyte-Colony Stimulating Factor (G-CSF)

Concomitant medications will be listed by patient.

7.6.5 Other Safety Analyses

7.6.5.1 Vital Signs

Vital sign data will be listed by patient for each time point. Summary statistics of vital signs and change from baseline may be tabulated where appropriate.

7.6.5.2 ECOG Performance Status

ECOG performance status will be summarized for each visit. Shifts from baseline to the lowest and highest post-baseline score will be tabulated.

7.6.5.3 ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) will be summarized by scheduled visit, and shifts from baseline will be tabulated.

7.7 Additional Analyses

7.7.1 Pharmacokinetics

Tisotumab vedotin antibody drug conjugate (ADC), total antibody (TAb), and MMAE concentrations will be summarized with descriptive statistics at each PK sampling time point. Selected PK parameters for ADC, TAb, and MMAE will be estimated by noncompartmental analysis (NCA) and summarized using descriptive statistics. The PK parameters will be tabulated using the PK analysis set which includes enrolled patients who received any amount of study drug and at least one PK parameter can be estimated. Data from this study may be combined with PK data from other clinical trials with tisotumab vedotin for population PK and PK/pharmacodynamic analyses.

7.7.2 Antitherapeutic Antibody (ATA)

The ATA incidence rate is defined as the proportion of patients who develop ATA at any time during the study. The ATA incidence rate will be summarized by cohort and total using the safety analysis set.

7.7.3 Biomarkers

Relationships of biomarker parameters (e.g., baseline values, absolute and relative changes from baseline) to efficacy, safety, and pharmacokinetic parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately in the Biomarker Analysis Plan.

7.7.4 Patient Reported Outcomes Analyses

Patient reported outcomes (PRO) as measured by NCI PRO-CTCAE and PROMIS will be summarized over time with descriptive statistics by visit using the FAS. For PRO-CTCAE, number and proportion of patients who experience a symptom with score >0 and with score of 3 or 4 will be summarized by symptom and visit. Shift tables comparing the highest post-baseline score to baseline score will be presented by symptom. Missing data will be summarized with the proportion of patients missing responses for each question.

The PROMIS Physical Function Scoring Manual will be used to calculate T-score and to impute missing data. The T-score and change from baseline will be summarized by visit. The number of missing questions at each visit will be summarized.

The compliance and completion rate of NCI PRO-CTCAE and PROMIS will be summarized for each assessment time point. Compliance rate is defined as the proportion of patients who completed the instrument among those who are expected to complete at a given visit. Completion rate is defined as the proportion of patients who completed the instrument among the FAS analysis set.

8 INTERIM ANALYSIS

A safety analysis will be conducted 28 days after all patients at the 0.9 mg/kg dose level in the safety run-in portion have received at least one dose of study treatment to evaluate the tolerability of the dose-dense regimen. If applicable, a second safety analysis will be conducted 28 days after all patients at the 1.2 mg/kg dose level have received at least one dose of study treatment. A safety monitoring committee (SMC), consisting of the investigators, study medical monitor, biostatistician, and drug safety representative, will review the safety data before proceeding to Parts A and B.

Interim analysis for futility will be performed on Part B after at least 20 patients with 1 to 3 prior lines of therapy, including bevacizumab treatment, have been treated and had at least one response assessment post-baseline.

The Bayesian predictive probability approach will be used to assess the futility criteria (Lee 2008). At the time of the interim futility analysis, the PPoS will be calculated. PPoS is the probability of achieving "success" should the cohort be continued to the maximum sample size of 60 in the target population (1 to 3 prior lines of therapy, including bevacizumab treatment) given the data observed at interim, and the cohort is considered "success" if the posterior probability that the ORR exceeds the response rate of current standard of care (i.e., 12% as reference in Section 3.2) is greater than 70%.

Both the confirmed and unconfirmed CR or PR observed at interim will be counted as a response for the calculation of PPoS. It is appropriate to include the unconfirmed response for the purpose of interim analysis because based on the estimates from GEN701 trial, about 60% of the responders will respond at their first post-baseline scan and approximately 75% of the confirmed/unconfirmed responses will eventually be confirmed. Table 1 summarizes the PPoS based on the number of responses observed among the first 20 patients.

Table 1: PPoS based on responses among the first 20 patients pretreated with bevacizumab

No. of responses* among the first 20 patients	PPoS
	PROC bevacizumab pretreated (p_0=12%)
0	*<1%*
1	*4%*
2	*20%*
3	*49%*
4	*77%*
5	*93%*
6	*99%*
7	*>99%*

8	*>99%*
9	*>99%*
10+	*>99%*

* P_0 is the response rate of current standard of care of each cohort

If the PPoS is <10% (i.e., 1 or fewer responses among the first 20 patients), the interim data indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the cohort and the cohort could be stopped early due to insufficient activity. On the other hand, if the PPoS is >70%, the interim data suggests that if the same trend continues, there is a high probability to conclude a "success" at the end of the cohort. The PFS, OS, and DOR will also be evaluated at the time of the interim futility analysis using Kaplan-Meier methodology. Based on the activity and safety data, together with the PPoS, the cohort may continue or be stopped early by the sponsor. A cohort or Part may also be discontinued at any point at the discretion of the sponsor.

The operating characteristics of the design based on 500,000 simulation runs are summarized in Table 2. If the true ORR is less than 5%, there is reasonable chance to reach the futility criterion at interim. On the other hand, if the true ORR is 20% or higher, the probability to stop for futility is low (<12%).

Table 2: Operating characteristics of predictive probability design

		Final Analysis (N=60) PROC bevacizumab-pretreated		
True ORR	Pr(Futility*)	Pr(obs. ORR ≥15%)	Pr(obs. ORR ≥20%)	Pr(obs. ORR ≥25%)
5%	74%	<1%	<1%	<1%
10%	39%	13%	1%	<1%
15%	18%	52%	17%	3%
20%	7%	84%	54%	20%
25%	2%	96%	84%	55%
30%	<1%	>99%	97%	84%
35%	<1%	>99%	>99%	96%

* 1 or fewer responders among the first 20 patients in the Part B bevacizumab pretreated cohort

Interim data from the study may be presented at scientific meetings such as the annual meetings of the American Society of Clinical Oncology and the European Society for Medical Oncology.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Original Protocol

Not Applicable.

9.2 Changes from the Original SAP

Update SAP version 2 to align with SGNTV-002 Protocol Amendment 4.

10 REFERENCES

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Appendix A IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

The algorithm below should be used to impute adverse event (AE) start dates for which only partial information is known. The algorithm should be applied to every AE record on a record by record basis. AE start dates should be imputed before imputation of AE condition end date in all cases. The AE condition end date should only be used in the imputation of the AE start date if it is a complete, known date.

AE day and month are missing

- If the year is the same as the year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was pre-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of study treatment)
- If the year is the same as the year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was post-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, first dose date of study treatment)
- If the year is before the year of first dose of study treatment:
  - AE start date will be imputed as the minimum of (AE condition end date*, December 31st see example 2 below)
- If the year is after the year of first dose of study treatment:
  - AE start date will be imputed as the minimum of (AE condition end date*, January 31st see example 2 below)

AE month only is missing

- Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

- If the month/year is the same as the month/year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was pre-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of study treatment)
- If the month/year is the same as the month/year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was post-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, first dose date of study treatment)
- If the month/year is before the month/year of first dose of study treatment:

- AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

- If the month/year is after the month/year of first dose of study treatment:
  - AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

* Only use condition end date if known and complete end date is available.

The following algorithm should be used to impute AE condition end dates. The AE records for a condition/event should be sorted by the imputed start dates then record position (order of entry into the eCRF). After sorting, if any condition end date month/year is greater than any subsequent record end date month/year, then change the imputed start day only to end of month. Repeat as necessary.

After sorting the AE records, apply the following rules to partial or missing AE condition end dates:

For all records excluding the last chronological record for a condition/event

- AE condition end date will be imputed as the start date of the subsequent record

For the last chronological record for a condition/event

- If outcome is "recovered/resolved", "recovered/resolved with sequelae", or "fatal" apply the following:
  - If only year is provided for the end date and year is equal to the year of the last dose date:
    - AE condition end date will be imputed as the minimum of (last dose date+30, death date, data extraction date, December 31st of the end date year)
  - If only year is provided for the end date and year is not equal to the year of the last dose date:
    - AE condition end date will be imputed as the minimum of (death date, data extraction date, December 31st of the end date year)
  - If month and year are provided for the end date:
    - AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year)
- If outcome is "recovering/resolving", "not recovered/resolved", "unknown", or blank:
  - AE condition end date will not be imputed.

Example 1

AESPID 1: Condition/Event HEADACHE
First dose date 01JAN2012

Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	15APR2012	1	not recovered/resolved	pre-ICF
15APR2012	UNMAY2012	2	recovering/resolving	post 1st dose
UNMAY2012	UNJUN2012	1	not recovered/resolved	post 1st dose
UNJUN2012	UNJUN2012	3	recovering/resolving	post 1st dose
UNJUN2012	10JUL2012	2	recovering/resolving	post 1st dose
10JUL2012	--	1	not recovered/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	15APR2012	1	not recovered/resolved
15APR2012	31MAY2012	2	recovering/resolving
31MAY2012	30JUN2012	1	not recovered/resolved
30JUN2012	30JUN2012	3	recovering/resolving
30JUN2012	10JUL2012	2	recovering/resolving
10JUL2012	--	1	not recovered/resolved

Example 2 (highlights choice of last day of the month as opposed to the 1st or the 15th)

AESPID 4: Condition/Event NAUSEA
First dose date 01APR2012

Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	25APR2012	1	not recovered/resolved	pre-ICF
25APR2012	UNAPR2012	2	recovering/resolving	post 1st dose
UNAPR2012	04MAY2012	1	recovered/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	25APR2012	1	not recovered/resolved
25APR2012	31APR2012	2	recovering/resolving
31APR2012	04MAY2012	1	recovered/resolved

Appendix B IMPUTATION OF PARTIALLY MISSING SUBSEQUENT ANTICANCER THERAPY START DATE

The algorithm below should be used to impute subsequent anticancer therapy start dates for which only day is missing.

- If the month and year of the start date of subsequent anticancer therapy are the same as the month and year of a response assessment date, and
    - If the response is a PD, subsequent anticancer therapy start date will be imputed as the response assessment date or the day after the last study treatment, whichever is later.
    - If the response is not a PD, subsequent anticancer therapy start date will be imputed as the first day of the month or the day after the last study treatment, whichever is later.
- Else if the month and year of the start date of subsequent anticancer therapy are the same as the month and year of the end date of last study treatment, subsequent anticancer therapy start date will be imputed as the day after the last study treatment end date.
- Else if the start date of subsequent anticancer therapy is later than the end date of last study treatment based on available month and year, subsequent anticancer therapy start date will be imputed as the first day of the month.