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Version:	Amendment 4, 24 August 2020
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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Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
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PROTOCOL SYNOPSIS

Protocol Number SGNTV-002	**Product Name** Tisotumab vedotin
Version Amendment 4, 24 Aug 2020	**Study Name** innovaTV 208
Phase 2	**Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

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

Study Objectives

The study objectives are to evaluate the safety, antitumor activity, and pharmacokinetics of tisotumab vedotin (TV) administered every 3 weeks (Q3W) or on Days 1, 8, and 15 of every 4-week cycle (3Q4W [dose-dense regimen]) for patients with epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer that has relapsed within 6 months of the completion of platinum-based treatment (hereafter collectively referred to as platinum-resistant ovarian cancer and abbreviated as PROC).

Primary Outcome Measures

- (Safety Run-In) Safety and tolerability of a dose-dense regimen of tisotumab vedotin, as measured by incidence of dose limiting toxicities (DLTs) or other unacceptable toxicities.
- (Parts A and B) Confirmed objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary Outcome Measures (Parts A and B)

- Safety and tolerability of tisotumab vedotin as measured by type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Confirmed and unconfirmed ORR (all responses)
- Cancer Antigen 125 (CA-125) response rate according to Gynecologic Cancer Intergroup (GCIG) criteria
- Overall response according to GCIG combined RECIST and CA-125 criteria
- Duration of response (DOR)
- Disease control rate (DCR), proportion of patients with complete response (CR), partial response (PR), or stable disease (SD). SD patients will be included if maintained for a minimum of 12 weeks.
- Time to response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Pharmacokinetic (PK) parameters and the incidence of antitherapeutic antibodies (ATA)

Additional (Parts A and B)

- Tissue Factor (TF) expression-response relationship
- Biomarkers of biological activity and resistance and predictive biomarkers of response
- In Part A and B US patients only, patient-reported outcomes as measured by an NCI PRO-CTCAE questionnaire customized to focus on visual symptoms, gastrointestinal symptoms, and bleeding, as well as Patient-Reported Outcomes Measurement Information System (PROMIS) version 2.0, short form 6b and other questions added by the sponsor.

Study Population

All patients must have PROC, defined as progression within 6 months from completion of platinum-containing therapy, and must be eligible for single agent chemotherapy. Safety run-in patients may have received more than 1 systemic treatment regimen for PROC. Patients eligible for Parts A and B patients must have received 1 to 3 prior anticancer lines of therapy overall, including at least 1 line of therapy containing bevacizumab or a biosimilar to bevacizumab.

Patients must have measurable disease at baseline according to RECIST v1.1. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate cardiovascular, central nervous system (CNS), renal, and hematological function (including coagulation parameters) are required at baseline. Patients may not have active bleeding conditions, uncontrolled pleural/pericardial effusions, uncontrolled tumor-related pain, peripheral neuropathy ≥ Grade 2, or ocular surface disease at the time of enrollment. Tumor TF expression will not be evaluated at screening or required for enrollment.

Number of Planned Patients

Approximately 222 patients may be enrolled in the study. This includes approximately 12 patients in the safety run-in phase as well as approximately 30 patients in each of 2 Part A cohorts with a possible expansion of up to approximately 70 additional 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.

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 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.

On a periodic basis, a Safety Monitoring Committee (SMC) will monitor the safety of patients participating in the trial. The SMC will be responsible for evaluating the results of safety analyses and will make

recommendations to the sponsor. Ongoing, real-time review of patient safety and serious adverse events (SAEs) will also be conducted by the sponsor's Drug Safety department throughout the study.

During the safety run-in period, the SMC will assess tolerability and safety of tisotumab vedotin (refer to SMC charter for additional details) at the end of the DLT period for each dose level. Ad hoc meetings of the SMC may be convened prior to the safety evaluation period if safety data indicate.

An individual's dose may be modified based upon treatment-related AEs. Response will be assessed every 6 weeks for the first 6 months, every 12 weeks for the next 6 months, and then every 6 months after that. RECIST v1.1 will be used by the investigator to score responses for primary and secondary endpoints as well as progression. Objective responses will be confirmed with repeat scans at least 4 weeks after the first documentation of response. The study will be closed 3 years after the last patient is enrolled or when no patients remain in long-term follow-up, whichever comes first. Additionally, the sponsor may terminate the study at any time.

Investigational Product, Dose, and Mode of Administration

For the dose-dense regimen, tisotumab vedotin will be administered at a dose of 0.9 mg/kg or 1.2 mg/kg as a 30–60 minute IV infusion on Days 1, 8, and 15 of every 4-week cycle. For patients weighing more than 100 kg, dosing will be capped at 90 mg or 120 mg for the 0.9 or 1.2 mg/kg doses, respectively, per infusion. If the dose for the dose-dense regimen is de-escalated to 0.65 mg/kg, the maximum dose will be capped at 65 mg per infusion.

For the Q3W regimen, tisotumab vedotin will be administered at a dose of 2.0 mg/kg as a 30–60 minute IV infusion on Day 1 of each 3-week treatment cycle. For patients weighing more than 100 kg, dosing will be capped at 200 mg per infusion.

Duration of Treatment

Patients will continue to receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anti-cancer therapy, study termination by the sponsor, pregnancy, or death, whichever comes first.

Efficacy Assessments

Antitumor activity will be assessed by radiographic tumor imaging at protocol-specified time points. Response assessment for primary and secondary efficacy endpoints will be evaluated by the investigator using RECIST v1.1. Patients will be followed for response assessments until disease progression, subsequent cancer therapy, consent withdrawal, study termination by the sponsor, or death, whichever comes first.

In addition to radiographic tumor assessments, expression level of CA-125 will also be monitored to assess response rate by CA-125 and the combination response of ORR/CA-125 as secondary endpoints.

Pharmacokinetic and Immunogenicity Assessments

Patient serum and plasma samples will be obtained for tisotumab vedotin PK and ATA evaluation at protocol specified- time points. Concentrations of tisotumab vedotin, total antibody, and monomethyl auristatin E (MMAE) will be measured in plasma and ATA in serum.

Biomarker Assessments

Blood and fresh and/or archival tumor samples will be collected at protocol-specified time points. Biomarker analysis will not be utilized for patient selection. Biomarker assessments in tumor tissue may include, but are not limited to: measurement of TF protein, mRNA expression, disease subtype, tumor immune microenvironment, and tumor mutational load. Assessments in blood may include, but are not limited to: cancer markers such as CA-125, cytokine measurements, abundance and phenotypes of immune cell subsets, and circulating nucleic acids. Methods of analysis may include immunohistochemistry (IHC), PCR and T-cell receptor beta chain sequencing, multiplex immune histofluorescence, mutation and gene expression profiling, Next Generation Sequencing, flow cytometry, and proteomic methodologies such as enzyme-linked immunosorbent assay (ELISA) and microvesicle- assessment.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, physical examination findings, eye examinations, vital signs, electrocardiograms (ECGs), concomitant medications, pregnancy testing, and laboratory tests. Safety assessments will be performed while the patient continues to receive treatment.

On a periodic basis, a safety monitoring committee (SMC) will monitor the safety of patients participating in the trial.

Statistical Methods

The primary analysis of the study will be performed when all treated patients have been followed for at least 6 months or come off study, whichever comes first. Patients enrolled in the safety run-in and Parts A and B of the study will be summarized separately.

Safety measurements will be summarized by descriptive statistics based on the safety analysis set. The safety analysis set will include all patients who received any amount of study treatment.

The primary endpoint of Parts A and B is the confirmed ORR per RECIST v1.1. The confirmed ORR will be estimated for each cohort based on the full analysis set, comprising all patients who received any amount of study treatment. The 95% exact confidence intervals (CIs) using the Clopper-Pearson method will be provided.

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

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%)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

3Q4W	three times every 4 weeks
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ASA	acetylsalicyclic acid
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the curve
β-hCG	beta human chorionic gonadotropin
CA 125	Cancer antigen 125
C_{max}	maximum concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EE	efficacy-evaluable
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
FAS	full analysis set
FIX	Factor IX
FVII	Factor VII
FX	Factor X
GCIG	Gynecologic Cancer Intergroup
HgbA1c	hemoglobin A1c
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous

MDRD	Modification of Diet in Renal Disease
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
OMP	ocular mitigation plan
ORR	objective response rate
OS	overall survival
PAR-2	protease activated receptor 2
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-L1	Programmed Death-Ligand 1
PE	pulmonary embolism
PFS	progression-free survival
PK	pharmacokinetic
PPoS	predictive probability of success
PR	partial response
PROC	platinum-resistant ovarian cancer
PT	prothrombin time
aPTT	active partial thromboplastin time
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
Scr	serum creatinine
SD	stable disease
SMC	Safety Monitoring Committee
TF	Tissue Factor
TTR	time to response
TV	tisotumab vedotin
ULN	upper limit of normal
VEGF	vascular endothelial growth factor

1 INTRODUCTION

1.1 Patient Population

Epithelial cancers of the ovary, fallopian tube, and of peritoneal origin in women exhibit similar biology, clinical characteristics and behavior. As such, these are often collectively referred to as epithelial ovarian cancer (EOC) in clinical trials and clinical practice.

Despite initial therapy, the vast majority of women with ovarian cancer will relapse and require subsequent therapy. Platinum-free interval is a strong predictor of treatment success in recurrent ovarian cancer (Pujade-Lauraine 2011). Patients whose disease relapses within 6 months after platinum-containing therapy are categorized as having platinum-resistant disease. At first relapse, approximately 25% of the patients have platinum-resistant ovarian cancer (PROC), and the vast majority of patients with recurrent disease will eventually develop PROC (Slaughter 2016).

Treatment combining double agent chemotherapy with the VEGF receptor antibody bevacizumab has become standard of care for women with PROC, despite a lack of evidence that it prolongs overall survival (OS) (Pujade-Lauraine 2014). Ideal patients for chemotherapy plus bevacizumab include those women who have received less than 2 prior regimens, have not received bevacizumab previously, and have no history of bowel obstruction within six months (Pujade-Lauraine 2014). For patients that relapse from or are not eligible for this combination treatment, options are limited primarily to single agent chemotherapy (Pujade-Lauraine 2014).

For patients who relapse after first-line therapy for PROC and are fit enough to receive subsequent treatment there is no standard of care. Clinical benefit, as measured by progressive-free survival (PFS) and OS, diminishes significantly below even the poor prognosis of first-line treatment as the line of therapy increases (Hanker 2012). Thus, there is an urgent need for more effective therapies for the treatment of PROC, particularly for patients previously treated with bevacizumab.

1.2 Tissue Factor

Human Tissue Factor (TF), also called 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 proangiogenic factors and proinflammatory mediators such as VEGF and interleukin-8.

Constitutive TF expression is mostly restricted to subendothelial cells (such as pericytes, smooth muscle cells and fibroblasts) that only interact with blood borne FVIIa when vascular integrity is compromised (Drake 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. Its 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 (Drake 1989; Flossel 1994; Imokawa 1997). Under pathological, inflammatory conditions TF is aberrantly expressed, including but not limited to bullous pemphigoid, urticaria (primarily on eosinophils), (Cugno 2009; Marzano 2011; Marzano 2009), inflammatory gastrointestinal diseases including Crohn's disease and ulcerative colitis (More 1993), and lung diseases including acute respiratory distress syndrome (Bastarache 2007).

1.2.1 Role of Tissue Factor in Malignancy

TF has a central physiological role in initiation of the coagulation cascade but, during oncological transformation, it is upregulated and expressed on the membranes of neoplastic cells and tumor-associated endothelial cells. Under pathological conditions, membranous TF can be aberrantly expressed. The pathological presence of TF in cancer cells promotes tumor initiated- thrombosis and cancer metastasis (Zhang 2017). Indications where tumor cells are known to express TF include gynecological and genito-urinary tumors such as cervical, ovarian, and prostate cancer as well as squamous cell carcinoma of the head and neck, non small- cell lung cancer, esophageal and colorectal tumors, breast cancer, malignant melanoma, and pancreatic cancer (Akashi 2003; Ohta 2002) (Chen 2010; Clouston 2016a; Clouston 2016b; Clouston 2016c; Cocco 2011a; Cocco 2011b; Khorana 2007; Sawada 1999; Uno 2007; Yokota 2009).

TF is expressed widely in ovarian cancer. In one study, TF was expressed in 27 of 32 (84%) of newly diagnosed ovarian cancer patients with stage I to IV disease. High TF expression correlated with incidence of venous thromboembolism (VTE), a common complication of ovarian cancer that occurs in as many as 42% of patients (Uno 2007) (Abu Saadeh 2013). The same association with VTE was found in a separate study that showed TF expression to be highest in clear cell carcinoma and endometroid carcinoma when compared with benign ovarian tumors (Abu Saadeh 2013). A different analysis reported TF expression in 24 of 25 (96%) ovarian cancer samples of stage I to IIIC disease, while no staining was found in normal ovarian tissue (Cocco 2011b). Immunohistochemical analysis of 48 primary ovarian tumor tissue microarrays showed membranous TF expression in 40% of these samples (sponsor's internal data).

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 (Han 2006; Nitori 2005; Patry 2008). Experimental studies suggest that tumor cells may benefit from both TF pro-coagulant activity and TF-induced PAR-2 signaling, for example through enhanced metastatic potential, angiogenesis, and cell survival (Kasthuri 2009; Ruf 1996). Furthermore, monoclonal antibodies that inhibit either TF:FVIIa intracellular signaling or TF pro-coagulant capacity could reduce tumor growth in vivo (Versteeg 2008).

1.3 Tisotumab Vedotin

Tisotumab vedotin is an antibody-drug conjugate (ADC) being developed for patients with tumors known to express TF, including ovarian cancer and other tumor types. It is composed of a TF-targeted human monoclonal immunoglobulin G1 (subtype κ) conjugated via a protease-cleavable valine citrulline linker to the drug monomethyl auristatin E (MMAE), a dolastatin 10 analog (Doronina 2003; Hamblett 2004; Sun 2005). Dolastatins and auristatins belong to a class of chemotherapies that act as microtubule disrupting agents.

1.3.1 Mechanism of Action

Tisotumab vedotin binds efficiently to human TF-expressing cells and is rapidly internalized into tumor cells where it undergoes lysosomal degradation resulting in release of the cytotoxic payload. Upon lysosomal degradation, tisotumab vedotin can induce bystander killing as a result of diffusion of free MMAE over the cell membrane, leading to cytotoxicity against neighboring tumor cells. In a biodistribution study in xenograft models, tisotumab vedotin effectively accumulated in TF-positive, but not TF-negative, tumors (sponsor's internal data).

1.3.2 Preclinical Experience with Tisotumab Vedotin

Tisotumab vedotin treatment resulted in potent and long-lasting tumor regression in TF expressing xenograft models derived from a variety of solid cancers, including -patient derived- xenograft models with heterogeneous TF expression. Moreover, potent tumor regression was observed in xenograft models of bladder, lung, cervical, and ovarian cancer that had received prior treatment with paclitaxel.

Due to the mode of action of tisotumab vedotin, its potential impact on TF-dependent coagulation was investigated in vitro in a series of coagulation assays. These included an activated factor X (FXa) generation assay, the standard prothrombin time assay, a clotting assay, thromboelastography (TEG), and a thrombin generation assay. Overall, only relatively minor impact of HuMax-TF on TF-mediated coagulation was observed. However, in vivo at clinically relevant or maximally tolerated doses of tisotumab vedotin in cynomolgus monkeys (≤5 mg/kg), no bleeding events were observed and prothrombin time and aPTT coagulation parameters were unaffected by treatment with tisotumab vedotin.

Tisotumab vedotin caused reversible skin changes in cynomolgus monkeys at doses of ≥5 mg/kg, but, apart from this, the safety profile was consistent with MMAE/tubulin-disrupting agents.

Further details on nonclinical studies can be found in the tisotumab vedotin Investigator's Brochure.

1.3.3 Clinical Experience With Tisotumab Vedotin

Tisotumab vedotin has been investigated in two Phase 1/2 clinical trials, GEN701 and GEN702. Each trial consists of a dose escalation part and a cohort expansion part. The dose escalation part has been finalized for both trials and the cohort expansion part is ongoing for

GEN701. Enrollment in GEN702 has discontinued. As of 17 August 2017, 207 patients had been enrolled across both trials.

GEN701

Dose escalation (Part I) has completed. A total of 27 patients were dosed, all on a Q3W schedule: 0.3 mg/kg (3 patients), 0.6 mg/kg (3 patients), 0.9 mg/kg (3 patients), 1.2 mg/kg (3 patients), 1.5 mg/kg (3 patients), 1.8 mg/kg (3 patients), 2.0 mg/kg (3 patients), and 2.2 mg/kg (6 patients). Among the 2.2 mg/kg dose group, 3 dose-limiting toxicities (DLTs) were reported in 3 patients (diabetes mellitus type II, mucositis, and neutropenic fever, all Grade 3). Based on these DLTs, the maximal tolerated dose (MTD) on a Q3W schedule was defined as 2.0 mg/kg.

Dose expansion (Part II) is ongoing. This portion of the study is an open label evaluation of the MTD of 2.0 mg/kg dosed Q3W in patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, squamous cell carcinoma of the head and neck, or NSCLC who have failed available standard therapy or who are not candidates for standard therapy. At the time of this data cut, 146 patients have been dosed with 2.0 mg/kg Q3W and 1 patient was dosed at 2.2 mg/kg Q3W.

GEN702

Dose escalation (Part I) has completed. A total of 9 patients were dosed using a dose-dense schedule: 0.9 mg/kg 3Q4W (3 patients) and 1.2 mg/kg 3Q4W (6 patients).

Dose expansion (Part II) has completed, with a total of 24 patients treated. Fourteen patients were treated at 1.2 mg/kg 3Q4W, 6 patients started at 1.2 mg/kg 3Q4W and were later switched to 2.0 mg/kg Q3W, and 4 received 2.0 mg/kg Q3W.

Pharmacokinetics

Based on preliminary pharmacokinetic (PK) analysis of data from GEN701 dose escalation at the 2.0 mg/kg dose, the mean (std dev, n) Cycle 1 maximum concentration (C_{max}) for ADC was 32.9 (7.3, n=3) ug/mL. The mean (std dev, n) Cycle 1 area-under-the-concentration-time curve from time zero to the last measurable concentration (AUC_{last}) was 54.5 (18.0, n=3) day*ug/mL. For MMAE, the mean (std dev, n) Cycle 1 C_{max} was 7.32 (4.5, n=3) ng/mL and the AUC_{last} was 78.2 (46.9, n=3) day*ng/mL.

Based on preliminary PK analysis of data from GEN702 dose escalation at the 0.9 mg/kg dose, the mean (std dev, n) Cycle 1 C_{max} for ADC was 20.4 (3.6, n=3) ug/mL and the AUC_{last} was 36.5 (6.40, n=3) day*ug/mL. For MMAE, the mean (std dev, n) Cycle 1 C_{max} was 1.69 (0.93, n=3) ng/mL and the AUC_{last} was 8.56 (4.1, n=3) day*ng/mL.

Based on preliminary PK analysis of data from GEN702 dose escalation at the 1.2 mg/kg dose, the mean (std dev, n) Cycle 1 C_{max} for ADC was 28.9 (3.5, n=6) ug/mL and the AUC_{last} was 60.4 (29.0, n=6) day*ug/mL. For MMAE, the mean (std dev, n) Cycle 1 C_{max} was 1.76 (1.38, n=6) ng/mL and the AUC_{last} was 9.72 (7.32, n=6) day*ng/mL.

1.3.3.1 Summary of Clinical Safety from GEN701 and GEN702

As of 17-Aug-2017, tisotumab vedotin had been administered to 174 patients dosed on a Q3W schedule in GEN701 and to 33 patients dosed 3Q4W and/or Q3W in GEN702 (207 total).

Based on combined safety data from the 2 trials and across all dose cohorts, the most commonly reported adverse events (AEs) seen in at least 41 patients (≥20%) were epistaxis (62%), fatigue (51%), nausea (44%), conjunctivitis and alopecia (38% each), decreased appetite and constipation (32% each), diarrhea (26%), vomiting (25%), peripheral neuropathy (22%), and abdominal pain (21%).

Grade 3 or higher AEs were reported in 120 patients (58%). Across all dose cohorts the most frequently reported Grade ≥3 AEs seen in at least four patients (2%) were fatigue (9%), anaemia (7%), hyponatraemia (5%), hypokalaemia, and abdominal pain (4% each), vomiting and conjunctivitis (3% each), nausea, intestinal obstruction, small intestinal obstruction, peripheral neuropathy, and symblepharon (2% each).

No AEs ≥ Grade 3 of coagulation abnormalities (prothrombin time [PT], activated partial thromboplastin time [aPTT], or international normalized ratio [INR]) have been reported.

Serious adverse events (SAEs) were reported in 96 patients (47%). Across all dose cohorts, the most frequently reported SAEs seen in at least four patients (2%) were abdominal pain (5%), vomiting and hyponatraemia (3% each), nausea, intestinal obstruction, small intestinal obstruction, general physical health deterioration, and anemia (2% each).

AEs leading to discontinuation were reported in 60 patients (29%). Across all dose cohorts the most frequent AEs leading to discontinuation were peripheral neuropathy (4%), conjunctivitis (3%), peripheral sensory neuropathy and symblepharon (2% each). All other AEs leading to discontinuation were reported in 2 patients (1%) each.

Five patients (3%) died within 30 days following the last dose of tisotumab vedotin in the GEN701 trial. Two patients died due to AEs considered to be related to tisotumab vedotin (pharyngeal tumor haemorrhage in a patient given 0.6 mg/kg and pneumonia in a patient given 2.0 mg/kg), 2 patients died as an outcome of disease progression not considered related to tisotumab vedotin, and one patient in the 2.0 mg/kg dose group died due to an unknown cause. One patient (3%) died within 30 days following last dose of tisotumab vedotin in the GEN702 trial due to disease progression.

Ocular Adverse Events

Ocular AEs are frequently reported with tisotumab vedotin. Events of conjunctivitis have been mainly CTCAE Grade 1 and 2. In May 2016, an initial ocular mitigation plan (OMP) was implemented upon reporting of the first case of Grade 3 conjunctivitis with irreversible damage in a patient given 0.9 mg/kg 3Q4W in the GEN702 trial. This plan was further updated in September 2016 after 2 patients in the GEN701 trial experienced Grade 2 conjunctivitis with conjunctival scarring. Due to an event of Grade 4 keratitis in the GEN701

dose expansion cohort (Part II), an urgent safety measure and a more comprehensive OMP were implemented across both GEN701 and GEN702 trials in December 2016. Elements of this ocular mitigation plan included the addition of ocular premedications for all patients (cooling eye pads during tisotumab vedotin infusion, vasoconstrictor eye drops immediately prior to treatment with study drug, prophylactic treatment with topical ophthalmic steroid eye drops, use of lubricating eye drops throughout study treatment) and dose modifications for ocular events.

Ocular AEs with Q3W tisotumab vedotin

As of 16 Aug 2019, 396 patients have received tisotumab vedotin on a Q3W schedule. The most frequent ocular AEs were conjunctivitis (29.5%), dry eye (20.7%), lacrimation increased (6.1%), vision blurred (6.1%), blepharitis (5.1%), and keratitis (4.8%).

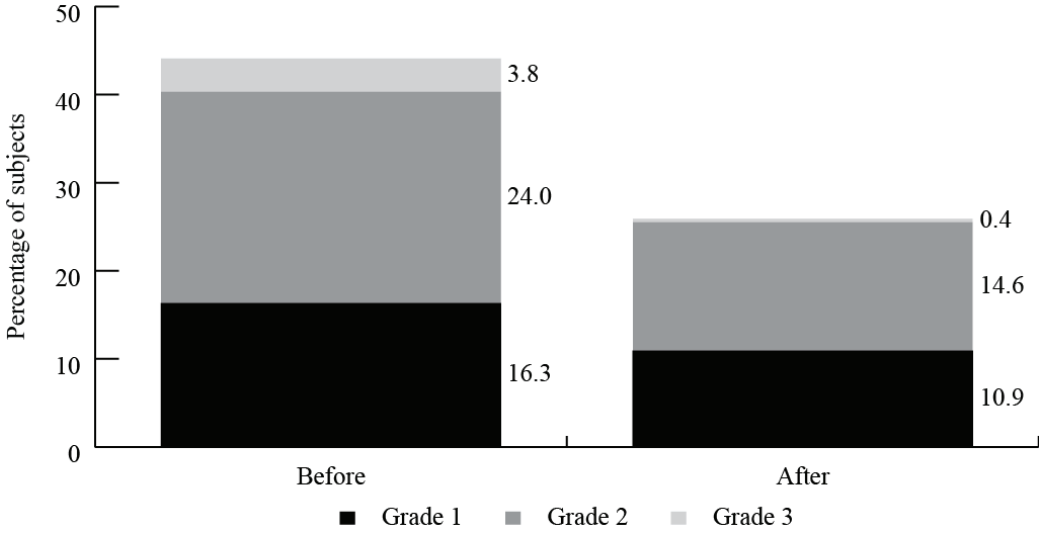
Since implementation of the December 2016 comprehensive OMP**,** both the frequency and severity of conjunctivitis, the most frequently reported ocular AE in relation to treatment with tisotumab vedotin, have been reduced. The frequency of conjunctivitis decreased from 44.2% to 25.9% in subjects dosed Q3W and only one subject has experienced a Grade 3 event after Dec-2016 (no Grade 4 or 5 events have been observed either before or after Dec-2016). Table 1 and Figure 1 summarize the decreased frequency and severity of conjunctivitis.

Table 1: Frequency of conjunctivitis* by CTCAE toxicity grading before and after Dec-2016 – subjects dosed Q3W

Maximum Grade	Before** (N=104) N (%)	After*** (N=274) N (%)	Total (N=378) N (%)
Any conjunctivitis event	46 (44.2)	71 (25.9)	117 (31.0)
Grade 1	17 (16.3)	30 (10.9)	47 (12.4)
Grade 2	25 (24.0)	40 (14.6)	65 (17.2)
Grade 3	4 (3.8)	1 (0.4)	5 (1.3)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)

* Including the preferred term ‘conjunctivitis’
** Including subjects that received first dose of tisotumab vedotin 1Q3W before 22-Dec-2016 OMP
*** Including subjects that received first dose of tisotumab vedotin 1Q3W after 22-Dec-2016 OMP

Figure 1: Frequency of the conjunctivitis* by CTCAE toxicity grading before and after Dec-2016 – subjects dosed Q3W



* Including the preferred term 'conjunctivitis'

All but one Grade 3 event of keratitis (including subjects dosed before and after Dec-2016) were non-serious events ≤ Grade 2. Events of ulcerative keratitis observed in subjects dosed Q3W have decreased in severity after implementation of the Dec-2016 OMP; one serious Grade 4 event was reported prior to Dec-2016 whereas no serious events of ulcerative keratitis have been reported in subjects dosed after Dec-2016 (all non-serious events were ≤Grade 2 with the exception of one event that was Grade 3).

Ocular AEs with Dose Dense Regimens

A total of 29 patients received 0.9 mg/kg or 1.2 mg/kg tisotumab vedotin on a dose-dense schedule in the GEN702 trial. None of the 3 patients treated with 3Q4W 0.9 mg/kg tisotumab vedotin were subject to the comprehensive ocular mitigation plan in the GEN702 study as all were treated prior to December 2016. One of the patients treated at 0.9 mg/kg 3Q4W experienced an event of Grade 3 conjunctivitis and Grade 2 symblepharon.

A total of 26 patients received 1.2 mg/kg 3Q4W tisotumab vedotin in the GEN702 trial. The 6 patients treated during dose escalation were treated prior to Dec 2016. The comprehensive OMP was inconsistently applied to the remaining 20 patients in the expansion cohort. Prophylactic steroid eye drops were not administered on subsequent dosing days after the first week for most patients. In addition, many patients with ongoing ocular events continued to receive tisotumab vedotin in GEN702 as they were treated prior to GEN702 Amendment 4, when dose adjustments due to ocular events became more restrictive. Grade 3 or higher ocular events were seen in 6 patients (23%) treated with 1.2 mg/kg tisotumab vedotin, including 5 patients (19%) with Grade 3 or higher symblepharon.

Since December 2016, the comprehensive ocular mitigation plan has been modified with additional measures for toxicity management (see Section 5.3.1).

For further details regarding clinical safety data with tisotumab vedotin, please refer to the Investigator Brochure.

Adverse Events of Special Interest

Three Adverse Events of Special Interest (AESI) have been identified:

- **Ocular AEs**: AEs of Grade 1-2 conjunctivitis are frequently reported in patients treated with tisotumab vedotin. Severe cases (≥ CTCAE Grade 3) of conjunctivitis, keratitis, and symblepharon have been observed in both trials. Implementation of a comprehensive mitigation plan and preventive measures (please refer to Section 5.3) have reduced both the frequency and severity of ocular adverse reactions in the GEN701 cohort expansion.
- **AEs of peripheral neuropathy**: (including preferred terms as: neuropathy peripheral; peripheral sensory neuropathy; peripheral motor neuropathy; polyneuropathy): Peripheral neuropathy is a well-known adverse reaction to treatment with chemotherapeutics (including cisplatin and taxanes) as well as MMAE-based ADCs and is frequently reported in relation to treatment with tisotumab vedotin. The majority of the reported cases are Grade 1–2; however, peripheral neuropathy was the leading cause of permanent discontinuation of study drug in GEN701 cohort expansion. A mitigation plan, including dose reduction and dose delays, is in place to control the rates and severity of peripheral neuropathy observed in patients treated with tisotumab vedotin (please refer to Section 5.3).
- **AEs of bleeding**: Bleeding events are considered AESI due to the target of tisotumab vedotin (TF). Epistaxis was the most common bleeding event, reported in 62% of patients across all dose cohorts (mainly Grade 1, one Grade 3 event). For the majority of the bleeding events (excluding epistaxis) no causal relation to treatment with tisotumab vedotin can be established. One serious event of Grade 5 pharyngeal hemorrhage was reported in a patient with SCCHN treated in the dose escalation cohort of GEN701. This event was considered most likely due to the patient's underlying disease. However, a causal relationship to trial drug could not be ruled out at that time. Please refer to Section 5.3 for dose modifications in the event of bleeding.

1.3.3.2 Summary of Efficacy Data from GEN701 and GEN702

Preliminary efficacy data

As of a data cutoff of 17 August 2017, 18% of patients in the GEN701 cohort expansion achieved response to tisotumab vedotin. The response rate varied across the indications ranging from 0% in prostate cancer to 32% in cervical cancer. Nine of the 11 responses in 34 cervical cancer patients were confirmed responses (26%).

Among 36 patients with ovarian cancer in the GEN701 cohort expansion, the objective response rate (ORR) was 17% (6 patients) with 3 confirmed responses (8% confirmed ORR). All of these patients were treated with tisotumab vedotin at 2.0 mg/kg on a Q3W schedule.

As of the final data cut date of 26 March 2018 in the GEN702 expansion, 12 patients with ovarian cancer who began treatment on the dose-dense schedule had an ORR of 33% (4 patients). Two of these 4 responses were confirmed (17% confirmed ORR). While all of these patients received 1.2 mg/kg tisotumab vedotin 3Q4W, 1 patient was switched onto 2.0 mg/kg tisotumab vedotin Q3W beginning at Cycle 6, after her response had been recorded. These limited data suggest that efficacy may be improved with a dose-dense schedule as compared to the Q3W schedule in patients with ovarian cancer. Though 3 patients received 0.9 mg/kg tisotumab vedotin on the dose-dense schedule in the GEN702 trial, none had ovarian cancer.

A complete summary of the clinical and nonclinical data relevant to tisotumab vedotin and its study in human patients is provided in the Investigator's Brochure.

1.4 Benefit Risk Assessment

Data from GEN701 and GEN702 demonstrate initial activity of tisotumab vedotin in heavily pretreated patients with recurrent or metastatic ovarian cancer who had received up to 6 lines of prior therapy. The most common AEs included epistaxis, fatigue, nausea, alopecia, conjunctivitis, constipation, decreased appetite, diarrhea, vomiting, and peripheral neuropathy. The majority of these events were mild to moderate (Grade 1 or 2).

Pharmacokinetic analysis indicates that dose intensity of the 0.9 mg/kg dose-dense and 2.0 mg/kg Q3W regimens is similar, allowing exploration of whether the more frequent schedule, with its different exposure profile, may improve efficacy. Limited data from a small number of patients treated with 3Q4W tisotumab vedotin in the GEN702 trial provide preliminary evidence that this exposure profile may, in fact, enhance efficacy as compared to Q3W dosing in ovarian cancer patients. The ORR was 17% in 36 ovarian cancer patients who received 2.0 mg/kg Q3W in GEN701 as opposed to an ORR of 33% in 12 patients who received 1.2 mg/kg 3Q4W in GEN702. The 1.2 mg/kg dose-dense regimen was associated with higher incidence of ocular adverse events in GEN702, including Grade 3 conjunctivitis and symblepharon. These patients were dosed without comprehensive prophylactic ocular safety mitigation measures (the comprehensive OMP) or ocular AE-related dose modifications used in current trials.

The following measures are being employed to ensure safety of patients in this trial:

- Safety run-in analysis of the dose-dense regimen of tisotumab vedotin with a 28 day safety evaluation period after the last patient is dosed.
- Identification of AESIs, including ocular adverse events, and implementation of preventative mitigation plans for each, when appropriate (see Section 5.3).

- A comprehensive ocular safety mitigation plan, including dose modifications and prophylactic measures, that is informed by progressive modifications to ocular preventive measures in the GEN701 and GEN702 trials, as well as ophthalmological thought leader input (see Section 5.4).
- Formation of a safety monitoring committee (SMC) to monitor safety of tisotumab vedotin in the selected patient populations.
- Interim futility analysis 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 interim futility analysis will ensure that further enrollment of these patients has reasonable potential to provide clinically meaningful benefit from tisotumab vedotin. While the futility analysis is being performed, enrollment in Part B will continue.

The feasibility of targeting TF in ovarian cancer with tisotumab vedotin has been demonstrated in the clinic in phase I studies in heavily pretreated populations with encouraging activity results. Preliminary safety and activity data from the GEN701 and GEN702 trials suggest a positive benefit-risk profile and warrant further investigation of tisotumab vedotin in ovarian cancer populations that exhibit high unmet medical need.

2 OBJECTIVES

This study will evaluate the safety, antitumor activity, and PK of tisotumab vedotin in patients with PROC. Specific objectives and corresponding endpoints for the study are summarized below (Table 2).

Table 2: Objectives and corresponding endpoints

Primary Objective	Corresponding Primary Endpoint
• (Safety run-in) Evaluate safety and tolerability of a dose-dense regimen of tisotumab vedotin	• Incidence of DLTs or other unacceptable toxicities
• (Parts A and B) Evaluate antitumor activity of tisotumab vedotin	• Investigator-determined confirmed ORR as measured by RECIST v1.1
Secondary Objectives (Parts A and B)	**Corresponding Secondary Endpoints**
• Evaluate the safety and tolerability of tisotumab vedotin	• Type, incidence, severity, seriousness, and relatedness of AEs
• Evaluate preliminary antitumor activity of tisotumab vedotin	• Investigator-determined confirmed and unconfirmed ORR as measured by RECIST v 1.1 (all responses)
• Evaluate antitumor activity of tisotumab vedotin	• CA-125 response rate • Combined RECIST/CA-125 overall response
• Evaluate durability of response in patients who respond to tisotumab vedotin	• Investigator- determined duration of response (DOR) as measured by RECIST v1.1
• Evaluate stability and control of disease	• Investigator-determined disease control rate (DCR) as measured by RECIST v1.1
• Evaluate the timing of responses	• Investigator- determined time to response (TTR) as measured by RECIST v1.1
• Evaluate PFS of patients treated with tisotumab vedotin	• Investigator- determined PFS as measured by RECIST v1.1
• Evaluate survival of patients treated with tisotumab vedotin	• Overall survival (OS)
• Assess pharmacokinetics of tisotumab vedotin	• Selected PK parameters for tisotumab vedotin and MMAE
• Assess immunogenicity of tisotumab vedotin	• Incidence of antitherapeutic antibodies (ATAs) to tisotumab vedotin
Additional Objectives (Parts A and B)	**Corresponding Additional Endpoints**
• Evaluate Tissue Factor expression-response relationship	• TF expression-response relationship following treatment with tisotumab vedotin
• Assess biomarkers of biological activity and resistance and predictive biomarkers of response	• Relationship between biomarkers in blood and tumor tissue to efficacy, safety, or other biomarker endpoints following treatment with tisotumab vedotin
• Patient-reported outcomes (Parts A and B, US patients only)	• 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

3 INVESTIGATIONAL PLAN

3.1 Summary of 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.

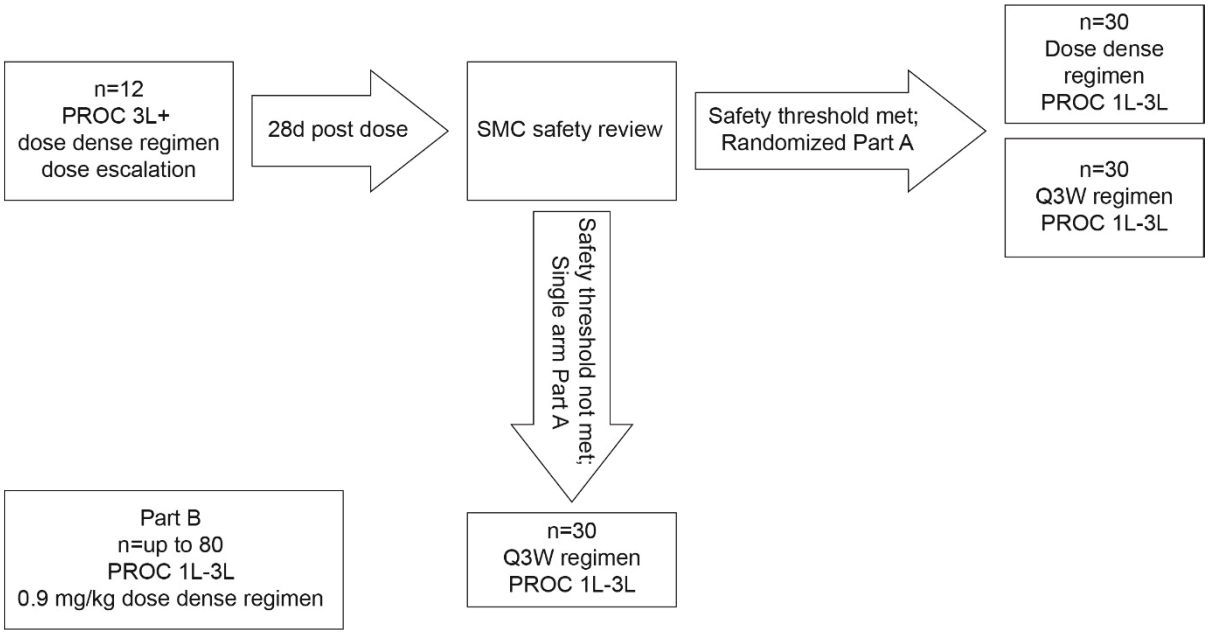
Interim futility analysis will be performed on Part B after at least 20 patients with 1 to 3 prior lines of therapy, including bevacizumab treatment, have been treated and had at least one response assessment post-baseline. The Bayesian predictive probability approach will be used to determine the futility criteria (Lee 2008). At the time of the interim futility analysis, the predictive probability of success (PPoS) will be calculated. Based on activity and safety data, together with the PPoS, the cohort may continue or be stopped early by the sponsor. While the interim futility analysis is performed, enrollment in Part B may continue. A cohort may also be discontinued at any point at the discretion of the sponsor.

On a periodic basis, a Safety Monitoring Committee (SMC) will monitor the safety of patients participating in the trial. The SMC will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. Ongoing, real-time review of patient safety and serious adverse events (SAEs) will also be conducted by the sponsor's Drug Safety department throughout the study.

During the safety run-in period, the SMC will assess tolerability and safety of tisotumab vedotin (refer to SMC charter for additional details) at the end of the DLT period for each dose level. Ad hoc meetings of the SMC may be convened prior to the safety evaluation period if safety data indicate.

An individual's dose may be modified based upon treatment-related AEs. Response will be assessed every 6 weeks for the first 6 months, every 12 weeks for the next 6 months, and then every 6 months after that. RECIST v1.1 will be used by the investigator to score responses for primary and secondary endpoints as well as progression. Objective responses will be confirmed with repeat scans at least 4 weeks after the first documentation of response. The study will be closed 3 years after the last patient is enrolled or when no patients remain in long-term follow-up, whichever comes first. Additionally, the sponsor may terminate the study at any time.

Figure 2: Study design



Safety run-in will start with 3Q4W dosing of 0.9 tisotumab vedotin in approximately 12 patients. If deemed safe, this dose will escalate to 1.2 mg/kg. If not deemed safe, it will de-escalate to 0.65 mg/kg. Part B will enroll only after the 0.9 mg/kg 3Q4W dose is deemed safe by the SMC.

3.1.1 Dose-Limiting Toxicity

DLTs will be assessed during the safety run-in portion of the study. Patients will be replaced for DLT evaluation if they do not complete the DLT evaluation period and do not experience a DLT before they discontinue from the study or start subsequent cancer therapy.

The DLT evaluation period for each safety run-in patient is defined as 28 days after the first dose of tisotumab vedotin. Patients who experience DLTs should not receive further treatment with tisotumab vedotin, unless clinical benefit is demonstrated with adequately managed toxicity. Subsequent treatment with tisotumab vedotin will be defined by the medical monitor in discussion with the site investigator in the context of the type of AE observed.

The IB for tisotumab vedotin describes AEs commonly observed, as well as less common serious findings. The IB should be referenced when attributing causality; however, the final decision regarding causality is at the discretion of the investigator.

A DLT is defined as:

One of the following that is observed within **28 days** of the first dose of tisotumab vedotin and is considered related to the drug:

- Grade 4 neutropenia (i.e., ANC $<0.5 \cdot 10^9$ cells/L) for minimal duration of seven days.
- Grade 3 and 4 febrile neutropenia (i.e., ANC $<1.0 \cdot 10^9$ 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 ($\leq 25.0 \cdot 10^9$ platelets/L).
- Grade 3 thrombocytopenia associated with bleeding episodes.
- Grade 3 or higher ocular adverse events
- Major bleeding, defined as:
  - Fatal bleeding
  - Symptomatic bleeding in a critical area organ, such as intracranial, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome
  - Bleeding causing a drop in hemoglobin level of 20 g/L (1.24 mmol/L) or more
  - Bleeding leading to transfusion of two or more units of whole blood or red cells.
- Stevens Johnson syndrome, toxic epidermal necrolysis, Grade ≥3 cutaneous vasculitis.
- Grade 3 neuropathy (not improving to Grade 1 within 3 weeks following end of treatment) 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.

3.2 Discussion and Rationale for Study Design

Therapies available to patients with PROC that have previously received 1 to 3 prior lines therapy, including bevacizumab, have poor response rates of around 12% in the first line setting and their effectiveness declines further in the second line and beyond. Long-term survival of patients with PROC is very low.

Patients with ovarian cancer have significant unmet medical need for therapies that can provide meaningful improvement. Tisotumab vedotin has been examined in a limited number

of patients with ovarian cancer in the GEN701 and GEN702 trials. These initial data show activity and need to be explored further in this population with high unmet need. Limited available data indicate that the dose-dense regimen may yield improved efficacy with the same or somewhat higher dose intensity as the Q3W regimen. Previously, dose-dense regimens, including 0.9 mg/kg and 1.2 mg/kg 3QW4, were tested in GEN702 patients without a comprehensive ocular mitigation plan, or strict dose modification guidelines for ocular toxicities in place. With appropriate ocular mitigation steps and dose-reduction guidelines, the dose dense schedule may be both tolerable and efficacious for this patient population.

3.2.1 Method of Assigning Patients to Treatment Groups

In the safety run-in portion of the study, each dose level will enroll sequentially starting at 0.9 mg/kg using the dose-dense schedule.

Part A will begin enrollment after the safety run-in period is completed. Patients will be randomly assigned to 1 of 2 dosing schedules in a 1:1 ratio. Randomization is intended to avoid bias and minimize imbalance between 2 dosing schedules on key prognostic factors for the purpose of evaluating safety and activity of the dose-dense and Q3W schedules. Randomization will be centrally controlled and stratified by first line vs. second line PROC and histology (serous vs. non-serous). At the time of randomization, a unique randomization number will be assigned to identify the dose regimen (dose-dense or Q3W) the patient is allocated to. Randomization procedures are detailed in the Study Manual.

Part B will have a single treatment arm and will begin enrollment of patients after 0.9 mg/kg dose-dense is deemed safe and tolerable in the safety run-in, if this occurs.

3.2.2 Rationale for Selection of Doses

Available data indicate that, across the GEN701 and GEN702 trials, patients with ovarian cancer experienced more tumor responses with a dose-dense schedule. However, in the GEN702 trial, ocular toxicities occurred at a higher rate with this schedule when dosed at 1.2 mg/kg. This necessitated the implementation of an initial ocular mitigation plan for patients in both trials who received tisotumab vedotin. The 0.9 mg/kg dose-dense schedule had been completed in the GEN702 trial before the comprehensive ocular mitigation plan had been put into place and therefore these patients did not receive these risk mitigations.

Ultimately, weekly dosing with 1.2 mg/kg tisotumab vedotin was halted in the GEN702 trial in favor of the 2.0 mg/kg Q3W regimen. The implementation of a comprehensive ocular mitigation plan in December 2016 as well as dose modifications for ocular AEs substantially reduced both the frequency and severity of ocular adverse reactions in patients treated at 2.0 mg/kg Q3W in the GEN701 cohort expansion.

Based on preliminary PK data from the dose escalation part of GEN701, at least 95% of tisotumab vedotin was eliminated from the plasma within 7 days of dosing across all investigated doses administered Q3W. Free MMAE was eliminated 14–21 days after administration. Based on preliminary PK data from GEN702 dose escalation at the 0.9 mg/kg

dose, no notable accumulation of mean ADC concentrations at day 7 post-dose, or area under the concentration-time curve from day 0 to day 7 (AUC_{0-7}), was observed between the first and last dose of Cycle 1 on a 3Q4W schedule (n=3).

Dose intensity of the 0.9 mg/kg dose-dense and 2.0 mg/kg Q3W regimens is similar, allowing exploration of whether a dose-dense schedule, with its different exposure profile, provides improved efficacy in ovarian cancer patients at the same dose intensity. Over a given cycle, the Q3W dose regimen at 2.0 mg/kg results in a dose intensity of 0.67 mg/kg/week, while the dose-dense regimen at 0.9 mg/kg 3 times every 4 weeks results in a dose intensity of 0.68 mg/kg/week. If DLTs are experienced in 2 or more patients at the 0.9 mg/kg dose during the safety run-in, a de-escalation of 28% to 0.65 mg/kg 3 times every 4 weeks will be explored. The 0.65 mg/kg dose level results in a dose intensity similar to a 1.5 mg/kg Q3W dose. In the GEN701 trial, at the 1.5 mg/kg Q3W dose, no DLTs were observed. Additionally, during dose escalation in the GEN701 trial, the 1.2 mg/kg Q3W dose was the lowest dose at which a partial response was observed, suggesting that 0.65 mg/kg 3 times every 4 weeks may be in the therapeutic range.

The full implementation of a comprehensive ocular mitigation strategy allows the re-exploration of the 1.2 mg/kg dose-dense regimen, if 0.9 mg/kg is deemed to be safe by the SMC. The 1.2 mg/kg dose-dense regimen represents an increase in dose intensity (33%) over the 0.9 mg/kg dose-dense regimen. The dose-dense regimens have lower maximum ADC plasma concentrations (C_{max}) and higher ADC trough plasma concentrations (C_{min}) compared to the 2.0 mg/kg Q3W dose regimen. These differences in pharmacokinetic profiles allow the further investigation of exposure-response relationships for optimal efficacy and safety.

3.2.3 Retreatment

Retreatment with tisotumab vedotin is not permitted.

3.2.4 Blinding and Unblinding

This is an open-label study.

4 STUDY POPULATION

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1 Inclusion Criteria

1. Histologic documentation of epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (excluding carcinosarcoma, mucinous, and low grade serous histologies), hereafter referred to as “ovarian cancer”.

2. Safety run-in patients only: Platinum-resistant ovarian cancer (PROC), which is defined as having progressed or relapsed within 6 months after previous platinum-containing chemotherapy and for which single agent chemotherapy is appropriate. Progression or

relapse must be documented radiographically using RECIST v1.1 criteria. The patient may have received more than 1 prior systemic treatment regimen in the PROC setting.

3. Part A and Part B patients only: PROC; with the following prior treatment requirements:
   - The patient must have received 1 to 3 prior anticancer lines of therapy overall, including at least 1 line of therapy containing bevacizumab or a biosimilar to bevacizumab.
   - Adjuvant ± neoadjuvant are considered 1 line of therapy.
   - Patients may have received a PARP inhibitor or an immuno-oncology (IO) agent; any of these regimens are to be considered a line of therapy for the purposes of this study if not used as maintenance therapy.
   - Maintenance therapy (including bevacizumab, PARP inhibitors and IOs) will be considered part of the preceding line of therapy and not to be counted as a new line of therapy.
   - Any chemotherapy regimen change due to toxicity in the absence of disease progression is considered as part of the same line of therapy.
   - Hormonal therapy will be not be counted towards the lines of therapy.

4. Measurable disease according to RECIST v1.1 as assessed by the investigator, defined as:
   a. A minimum of one non-nodal lesion ≥10 mm in the longest diameter 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 upon approval of the sponsor's medical monitor.

      OR

   b. Lymph node lesion ≥15 mm in the shortest diameter from a non-irradiated area.

5. Age 18 years or older.

6. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (see Appendix E for conversion of performance status using Karnofsky and Lansky scales, if applicable).

7. The following baseline laboratory data:
   - Absolute neutrophil count (ANC) ≥1500/µL assessed at least 2 weeks after growth factor support, if applicable.
   - Platelet count ≥100 x 10^9/L assessed at least 2 weeks after transfusion with blood products.
   - Hemoglobin ≥5.6 mmol/L (9.0 g/dL) assessed at least 2 weeks after transfusion with blood products.
   - Serum bilirubin ≤1.5 x upper limit of normal (ULN) or direct bilirubin ≤2 x ULN in patients diagnosed with Gilbert's syndrome.

- Estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) study equation as applicable.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN. (If liver tumor/metastases are present, then <5 x ULN is allowed).

8. Acceptable coagulation status:
   - INR ≤1.2 without anticoagulation therapy.
   - aPTT ≤1.25 ULN.
9. Life expectancy of at least 3 months.
10. Patients of childbearing potential as defined in Section 4.3, under the following conditions:
    - Must have a negative serum or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to the first dose of tisotumab vedotin. Patients with false positive results and documented verification that the patient is not pregnant are eligible for participation.
    - Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug administration.
    - Must agree to complete abstinence or, if sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (as defined in Appendix F) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
11. Able to provide fresh or archival tissue for biomarker analysis. Fresh tissue must be obtained from a newly obtained core or excisional biopsy of a tumor lesion. Archived specimens must have been collected within 2 years of first administration of tisotumab vedotin. Older specimens may be allowed upon approval of the sponsor's medical monitor.
12. The patient or the patient's legally authorized representative must provide written informed consent.

4.2 Exclusion Criteria

1. Primary platinum-refractory disease, defined as disease progression within 3 months of completion of first line platinum-based therapy.
2. Patients with clinical symptoms or signs of gastrointestinal obstruction within the past 6 months or who currently require parenteral nutrition.

3. 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 8 weeks of trial entry.
4. Cardiovascular: Clinically significant cardiac disease including uncontrolled hypertension (systolic BP >150 mmHg or diastolic BP >90 mmHg), unstable angina, acute myocardial infarction within 6 months prior to screening, serious cardiac arrhythmia requiring medication (not including asymptomatic atrial fibrillation with controlled ventricular rate); any medical history of congestive heart failure (Class II or higher as classified by the New York Heart Association, see Appendix H), or any medical history of decreased cardiac ejection fraction of <45%.
5. Ophthalmological: Active ocular surface disease at baseline. An ocular evaluation is to be confirmed by an ophthalmologist at screening. Patients with any prior episode of cicatricial conjunctivitis or Stevens Johnson syndrome (as evaluated by the investigator) are ineligible. Cataract is not considered active ocular surface disease for this study.
6. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, ductal carcinoma in situ, or stage I uterine cancer.
7. Inflammatory bowel disease including Crohn's disease and ulcerative colitis.
8. Ongoing, acute, or chronic inflammatory skin disease.
9. Uncontrolled tumor-related pain.
10. Inflammatory lung disease, including moderate and severe asthma and chronic obstructive pulmonary disease, requiring chronic medical therapy.
11. Grade 3 or higher pulmonary disease unrelated to underlying malignancy.
12. Patients with significant peripheral vascular disease.
13. Uncontrolled pleural or pericardial effusions.
14. Medications or treatment regimens:
    - A patient may not receive both anticoagulant(s) and antiplatelet agent(s) concurrently while on study.
    - Cumulative dose of corticosteroid ≥150 mg (prednisone or equivalent doses of corticosteroids) within 2 weeks of the first tisotumab vedotin administration is prohibited.

15. Surgery/procedures: Major surgical procedure (defined as a surgery requiring inpatient hospitalization of at least 48 hours) within 4 weeks or excisional biopsy within 7 days prior to the first study drug administration. Patients who have planned major surgery during the treatment period must be excluded from the trial.

16. Received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

17. Peripheral neuropathy Grade ≥2

18. Prior therapy:

    - Any prior treatment with MMAE-derived drugs.
    - Radiotherapy within 21 days prior to the first administration of study drug. Patients must have recovered from all radiation-related toxicities. At least 42 days must have elapsed from the last administration of chemo-radiotherapy.
    - Small molecules, chemotherapy, immunotherapy, biologics, experimental agents, or any other antitumor therapy within 21 days prior to the first administration of study drug. If underlying disease is progressing on treatment, patients may enroll within 21 days upon approval of the sponsor's medical monitor. These patients must have recovered from all related toxicities.

19. Any uncontrolled Grade 3 or higher (per the NCI CTCAE v5.0) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of tisotumab vedotin. Routine antimicrobial prophylaxis is permitted.

20. Known seropositivity of human immunodeficiency virus; known medical history of Hepatitis B or C infection.

    - Note: No testing for human immunodeficiency virus, Hepatitis B, or Hepatitis C is required unless mandated by local health authorities.

21. Known history of untreated brain metastasis or active brain metastasis. Patients with symptoms of brain metastasis should be screened for this condition prior to enrollment.

22. Patients who are breastfeeding, pregnant, or planning to become pregnant from time of informed consent until 6 months after final dose of study drug administration.

23. Known hypersensitivity to any excipient contained in the drug formulation of tisotumab vedotin.

24. Other serious underlying medical condition that, in the opinion of the investigator, would impair the patient's ability to receive or tolerate the planned treatment and follow-up.

4.3 Childbearing Potential

A person of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes.

4.4 Removal of Patients from Therapy or Assessment

Seattle Genetics or their designee must be notified if a patient is withdrawn from study treatment (discontinuation) or from the study (withdrawal). The reason(s) for withdrawal must be documented in the patient's medical records and case report form (CRF).

4.4.1 Discontinuation of Study Treatment

A patient's study treatment may be discontinued for any of the following reasons:

- Progressive disease (PD)
- Adverse event (AE)
- Pregnancy
- Investigator decision
- Patient decision, non-AE (consent withdrawal)
  Note: Ensure that patients who decide to stop treatment **because of an AE** are not included in this rationale.
- Study termination by sponsor
- Subsequent cancer therapy
- Other, non-AE

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

4.4.2 Patient Withdrawal from Study

Any patient may be discontinued from the study for any of the following reasons:

- Patient withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

Patients in the safety run-in portion of the study will receive tisotumab vedotin at a dose of 0.9 mg/kg or 1.2 mg/kg as a 30–60 minute intravenous (IV) infusion on Days 1, 8, and 15 of

every 4-week treatment cycle. For patients weighing more than 100 kg, dosing will be capped at 90 mg per infusion. If the dose is escalated to 1.2 mg/kg, dosing will be capped at 120 mg per infusion. If the dose is de-escalated to 0.65 mg/kg, dosing will be capped at 65 mg per infusion.

Patients in Part A will be randomized to receive either the RP2D dose-dense regimen from the safety run-in portion of the study or 2.0 mg/kg tisotumab vedotin administered as a 30–60 minute IV infusion on Day 1 of each 3-week treatment cycle (Q3W regimen). For patients weighing more than 100 kg, dosing will be capped at 200 mg per infusion.

Patients in Part B will receive 0.9 mg/kg tisotumab vedotin as a 30–60 minute intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle. For patients weighing more than 100 kg, dosing will be capped at 90 mg per infusion.

5.2 Investigational Product

Detailed information describing the preparation, administration, and storage of tisotumab vedotin is located in the Pharmacy Instructions.

5.2.1 Description

Tisotumab vedotin is presented as lyophilized powder for reconstitution in water for injection and is intended for IV dosing by infusion after dilution in physiological saline solution. It is manufactured and provided under the responsibility of the sponsor. A list of excipients can be found in the Investigator's Brochure.

5.2.2 Dose and Administration

Tisotumab vedotin will be administered as an infusion given over approximately 30–60 minutes. In the absence of infusion-related reactions (IRRs), the infusion rate for all patients should be calculated in order to achieve a 30–60 minute infusion period. **Tisotumab vedotin must not be administered as an IV push or bolus.** Tisotumab vedotin should not be mixed with other medications.

Weight-based dosing is based on the patient's actual body weight. Doses must be adjusted for patients who experience a ≥10% change in weight from baseline. Patient weight must be measured during all relevant assessment windows as described in the schedule of events. Other dose adjustments for changes in body weight are permitted per institutional standard. Rounding is permissible to the nearest kilogram.

An exception to weight-based dosing is made for patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted per infusion in this study is 90 mg or 120 mg for patients receiving the dose-dense regimen and 200 mg for patients receiving the Q3W regimen. If dosing is de-escalated to 0.65 mg/kg for patients on the dose-dense regimen, the maximum dose permitted per infusion for these patients will be 65 mg.

5.2.3 Dose Modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose reductions are permitted in order to allow the patient to continue tisotumab vedotin treatment. Dose reductions must be preapproved by the sponsor's medical monitor unless allowed according to the mitigation plans specified in the protocol (please refer to Section 5.3). Once a dose is reduced, it should not be re-escalated for that patient during the study.

- If toxicities occur on Day 1 of any cycle and require the tisotumab vedotin dose to be held, then the start of the cycle may be delayed.
- If toxicities occur on Day 8 and require the dose to be held for >2 days, then the dose should be eliminated.
- If toxicities occur on Day 15 of any cycle and require the dose to be held >7 days, then the dose(s) should be eliminated.
- If a patient only receives tisotumab vedotin on Day 1 and needs to skip Days 8 and 15, the patient could resume the next cycle as early as Day 22 (new Day 1) per the mitigation plans specified in Section 5.3.

In case any dose reduction of tisotumab vedotin is needed, the dose must be reduced according to the guidelines provided below (Table 3 and Table 4)

Table 3: Dose modification scheme: Dose-dense regimen

Previous dose of tisotumab vedotin	Reduced dose of tisotumab vedotin
1.2 mg/kg (120 mg maximum total dose) on D1, D8, and D15	0.9 mg/kg (90 mg maximum total dose) on D1, D8, and D15
0.9 mg/kg (90 mg maximum total dose) on D1, D8, and D15	0.65 mg/kg (65 mg maximum total dose) on D1, D8, and D15
0.65 mg/kg (65 mg maximum total dose) on D1, D8, and D15	0.65* mg/kg (65 mg maximum total dose) on D1 and D8

* If the patient is already being treated with tisotumab vedotin 0.65 mg/kg on D1 and D8, the dose must not be reduced further.

Table 4: Dose modification scheme: Q3W regimen

Previous dose of tisotumab vedotin	Reduced dose of tisotumab vedotin
2.0 mg/kg (200 mg maximum total dose)	1.3 mg/kg (130 mg maximum total dose)
1.3 mg/kg (130 mg maximum total dose)	0.9* mg/kg (90 mg maximum total dose)

* If the patient is already being treated with tisotumab vedotin 0.9 mg/kg, the dose must not be reduced further.

Any dose delay(s) must be pre-approved by the sponsor's medical monitor unless allowed according to the mitigation plans specified in Section 5.3. Tisotumab vedotin dosing can be resumed immediately after the adverse event has improved as indicated in the mitigation plans or as agreed with sponsor. Tisotumab vedotin must be permanently discontinued for any dose delay >12 weeks, (i.e., 84 days calculated from the intended day of the next scheduled dose), unless approved by the sponsor.

5.3 Mitigation Plans for Specific Adverse Events

5.3.1 Ocular Adverse Events

All patients must adhere to all ocular premedication guidelines for tisotumab vedotin (refer to Section 5.4).

Dose modification and toxicity management guidelines for ocular AEs are provided in Table 5. Dose modification and toxicity management guidelines for ocular AEs should be based upon CTCAE v5.0 grading.

If a patient experiences an ocular AE, every effort must be made to refer the patient for ophthalmological evaluation within 3 days. The ophthalmologist's objective findings and overall evaluation should be recorded in the electronic case report form (eCRF). The patient should hereafter be followed closely by the ophthalmologist until resolution. Topical treatment should be initiated by the ophthalmologist according to the treatment guidelines in Table 5.

All ocular events should be graded according to the following:

- 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 5.0). Please note that grading should be based upon treatment emergent criteria listed in CTCAE (i.e., not taking prophylactic premedication into consideration).

Table 5: Dose modification and toxicity management guidelines – ocular AEs

AE and Toxicity Grade (CTCAE v5.0)	Action Taken with Tisotumab Vedotin	Guidelines for Treatment Prescribed by the Ophthalmologist
Conjunctivitis		
Conjunctivitis Grade 1	Hold dosing until event is managed effectively. Continue tisotumab vedotin at the same dose level.	Local ophthalmologist must prescribe frequent dosing of topical steroid drops.
Conjunctivitis Grade 2 1st occurrence	Hold dosing until event has improved to ≤Grade 1. Continue tisotumab vedotin at the same dose level.	Local ophthalmologist must prescribe frequent dosing of topical steroid drops (prednisolone 1% or equivalent, overnight treatment with a topical steroid ophthalmic ointment, such as loteprednol etabonate, can be considered). Prophylaxis with topical antibiotic drops should be also be considered. Additional treatment modalities such as topical lubricating drops, topical immunomodulator drops (such as calcineurin inhibitors or equivalent), treatment with systemic steroids or surgical intervention to be determined as clinically applicable by the local ophthalmologist. Treatment to continue until the local ophthalmologist deems necessary.
Conjunctivitis Grade 2 2nd occurrence	Hold dose of tisotumab vedotin: • If the event has improved to baseline within 6 weeks (calculated from the onset date of the 2nd Grade 2 event), reduce next dose of tisotumab vedotin according to Section 5.2.3. If the event does not improve to baseline within 6 weeks, permanently discontinue tisotumab vedotin.	
Conjunctivitis Grade 2 3rd occurrence	Permanently discontinue tisotumab vedotin.	
Conjunctivitis ≥Grade 3	Permanently discontinue tisotumab vedotin.	
Keratitis		
Keratitis Grade 1	Hold dosing until event is managed effectively. Continue same dose for next dosing	Local ophthalmologist must prescribe frequent dosing of topical steroid drops.
Keratitis Grade 2 1st occurrence	Hold tisotumab vedotin until event has improved to ≤Grade 1. Reduce tisotumab vedotin according to Section 5.2.3.	Local ophthalmologist must prescribe frequent dosing of topical steroid drops (prednisolone 1% or equivalent, overnight treatment with a topical steroid ophthalmic ointment, such as loteprednol etabonate, can be considered). Prophylaxis with topical antibiotic drops should be also be considered. Additional treatment modalities such as topical lubricating drops, topical immunomodulator drops (such as calcineurin inhibitors or equivalent), treatment with systemic steroids or surgical intervention to be determined as clinically applicable by the local ophthalmologist. Treatment to continue until the local ophthalmologist deems necessary.
Keratitis ≤Grade 2 2nd occurrence	Hold tisotumab vedotin until event has improved to ≤Grade 1. Reduce tisotumab vedotin again according to Section 5.2.3.	
Keratitis ≤Grade 2 3rd occurrence	Permanently discontinue tisotumab vedotin.	
Keratitis ≥Grade 3	Permanently discontinue tisotumab vedotin.	

AE and Toxicity Grade (CTCAE v5.0)	Action Taken with Tisotumab Vedotin	Guidelines for Treatment Prescribed by the Ophthalmologist
Conjunctival ulceration and opthalmological findings of fluorescent patches must be handled as below		
Grade 1–2 1st occurrence	Hold tisotumab vedotin until event is managed effectively. Reduce tisotumab vedotin according to Section 5.2.3.	Local ophthalmologist must prescribe frequent dosing of topical steroid drops (prednisolone 1% or equivalent, overnight treatment with a topical steroid ophthalmic ointment, such as loteprednol etabonate, can be considered). Prophylaxis with topical antibiotic drops should be also be considered. Additional treatment modalities such as topical lubricating drops, topical immunomodulator drops (such as calcineurin inhibitors or equivalent), treatment with systemic steroids or surgical intervention to be determined as clinically applicable by the local ophthalmologist. Treatment to continue until the local ophthalmologist deems necessary.
Grade 1–2 2nd occurrence	Hold tisotumab vedotin until event is managed effectively. Reduce tisotumab vedotin according to Section 5.2.3.	
Grade 1–2 3rd occurrence	Permanently discontinue tisotumab vedotin	Consult local ophthalmologist immediately.
≥Grade 3	Permanently discontinue tisotumab vedotin	Consult local ophthalmologist immediately.
Symblepharon must be handled as below		
Any grade	Permanently discontinue tisotumab vedotin.	Consult local ophthalmologist immediately.
All other ocular toxicities (e.g., dry eye, vision blurred, blepharitis, lacrimation increased, etc.)		
All other ocular toxicities Grade 1	Hold dosing until event is managed effectively. Continue tisotumab vedotin at the same dose level.	If clinically indicated, local ophthalmologist must prescribe frequent dosing of topical steroid drops (prednisolone 1% or equivalent, overnight treatment with a topical steroid ophthalmic ointment, such as loteprednol etabonate, can be considered). Prophylaxis with topical antibiotic drops should be also be considered. Additional treatment modalities such as topical lubricating drops, topical immunomodulator drops (such as calcineurin inhibitors or equivalent), treatment with systemic steroids or surgical intervention to be determined as clinically applicable by the local ophthalmologist. Treatment to continue until the local ophthalmologist deems necessary.
All other ocular toxicities Grade 2 1st occurrence	Hold dosing until event has improved to ≤Grade 1 Continue tisotumab vedotin at the same dose level	
All other ocular toxicities Grade 2	Hold dose of tisotumab vedotin: • If the event has improved to baseline within 6 weeks (calculated from the onset date of the 2nd occurrence of the Grade 2 event), reduce next dose of tisotumab vedotin according to Section 5.2.3.	

AE and Toxicity Grade (CTCAE v5.0)	Action Taken with Tisotumab Vedotin	Guidelines for Treatment Prescribed by the Ophthalmologist
All other ocular toxicities Grade 2 2nd occurrence	If the event does not improve to baseline within 6 weeks, permanently discontinue tisotumab vedotin.	
All other ocular toxicities Grade 2 3rd occurrence	Permanently discontinue tisotumab vedotin.	Consult local ophthalmologist immediately.
All other ocular toxicities ≥Grade 3	Permanently discontinue tisotumab vedotin.	Consult local ophthalmologist immediately.

5.3.2 Infusion-Related Reactions

Tisotumab vedotin may cause IRRs including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion.

- In case any clinical significant IRR is observed during or after the first infusion of tisotumab vedotin or at subsequent treatment cycles, the patient should be observed for 2 hours after the end of tisotumab vedotin administration for all subsequent infusions.
- At all times during infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents must always be available along with equipment for assisted ventilation.
- All premedication must be reported on the concomitant medication page in the eCRF.

Dose modification and toxicity management guidelines for tisotumab vedotin associated infusion reaction are provided in Table 6.

Table 6: Dose modification and toxicity management for infusion-related reactions

Infusion-Related Reactions (IRRs)	
Grade 1	Continue infusion at the investigator's discretion at half the infusion rate under close medical supervision.
Grade 2	Infusion must be interrupted and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision, if symptoms have resolved to ≤Grade 1 within an hour. The patient should be pre-medicated (antihistamine, acetaminophen and corticosteroids are recommended) before the next infusion.
Grade 3 1st occurrence	Infusion must be interrupted and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to ≤Grade 1 within an hour. The patient should be pre-medicated (antihistamine, acetaminophen and corticosteroids are recommended) before the next infusion.
Grade 3 2nd occurrence despite premedication	Permanently discontinue tisotumab vedotin treatment.
≥Grade 4	Infusion must be interrupted immediately and appropriate medical therapy must be administered. Permanently discontinue tisotumab vedotin treatment.

5.3.3 Other Adverse Events

AEs such as increased bleeding, hemorrhage, elevated liver enzymes, mucositis, neutropenia, and peripheral neuropathy may be associated with tisotumab vedotin administration. Dose modification and toxicity management are provided in Table 7.

Table 7: Dose modification and toxicity management for other AEs associated with tisotumab vedotin

Bleeding Events	
• Control vital signs and ensure stabilization of the patient according to local standards. • Prompt evaluation to identify the underlying etiology of the bleeding event. Management should ultimately be dictated by the underlying diagnosis. • Control laboratory coagulation and hematologic parameters including PT, aPTT, fibrinogen, platelets, INR and hemoglobin as soon as possible.	
All Patients	
Any grade pulmonary or CNS hemorrhage	Permanently discontinue tisotumab vedotin treatment.
Patients NOT on anticoagulation therapy	
1st occurrence Hemorrhage (other)[1] Grade 3	Hold dosing until: a) Bleeding has resolved. b) Blood hemoglobin level is stable. c) There is no bleeding diathesis that could increase the risk of continuing therapy. d) Patients must not have tumors involving or adjacent to major blood vessels When the above criteria are fulfilled the patient can resume treatment with tisotumab vedotin at the same dose as prior to the event.
≥2nd occurrence Hemorrhage (other)[1] Grade 3	Contact sponsor in order to discuss whether the patient may continue or must permanently discontinue tisotumab vedotin treatment.
Hemorrhage Grade 4 (any occurrence)	Patient must permanently discontinue tisotumab vedotin treatment
Patients on anticoagulation therapy	
INR >2.5	Patients on therapeutic anticoagulation whose INR is >2.5 prior to infusion of tisotumab vedotin must hold tisotumab vedotin until INR is ≤2.5. Patients may resume tisotumab vedotin administration immediately after the INR is ≤2.5. Strongly consider holding anticoagulation until the above parameters are met.
Hemorrhage (other)[a] Grade 3	Hold anticoagulation therapy. Contact sponsor in order to discuss whether the patient may continue or must permanently discontinue tisotumab vedotin treatment.
Hemorrhage Grade 4 (any occurrence)	Patient must permanently discontinue tisotumab vedotin treatment
Liver parameters elevated (AST, ALT, or bilirubin)	
≥Grade 3	Hold tisotumab vedotin until toxicity resolves to ≤Grade 1. In the event of recurrence of ≥Grade 3, permanently discontinue tisotumab vedotin.
Mucositis	
Grade 3	Hold tisotumab vedotin until event has improved to ≤Grade 2, then reduce tisotumab vedotin according to Section 5.2.3. Treat according to local practice. In the event of recurrence to Grade 3, permanently discontinue tisotumab vedotin.
Grade 4	Permanently discontinue tisotumab vedotin.

Neutropenia	
Grade 3 or 1st occurrence of Grade 4	Hold tisotumab vedotin until event has improved to ≤Grade 2 (including G-CSF administration). Growth factor support (G-CSF) should be given prophylactically prior to subsequent tisotumab vedotin administrations.
2nd occurrence Grade 4	Contact sponsor to discuss dose reduction or discontinuation of tisotumab vedotin.
Peripheral neuropathy (including preferred terms as: neuropathy peripheral; peripheral sensory neuropathy; peripheral motor neuropathy; polyneuropathy)	
Grade 2 and 3 Initial or worsening of pre-existing condition	Hold tisotumab vedotin until event has improved to ≤Grade 1. Reduce next dose according to dose reduction scheme in Section 5.2.3.
≥Grade 4	Permanently discontinue tisotumab vedotin.

a Any other hemorrhage with the exception of pulmonary or CNS hemorrhage.

5.3.4 Storage and Handling

Refrigeration should be set at 2–8°C for storage of vials and solutions containing tisotumab vedotin. The controlled location must be accessible only to the pharmacist, the investigator, or a duly designated person. Tisotumab vedotin does not contain preservatives; therefore, opened and reconstituted vials should be used within 24 hours of preparation. If not used immediately, the in-use storage should not be longer than 24 hours. It is recommended that tisotumab vedotin vials and solutions be stored protected from direct sunlight until the time of use. Reconstituted vials must not be shaken.

Drug accountability procedures are provided in the Pharmacy Binder.

5.3.5 Packaging and Labeling

Tisotumab vedotin will be supplied in vials containing 40 mg of tisotumab vedotin as lyophilized powder. The powder must be reconstituted with 4 mL water for injection leading to a 10 mg/mL solution. Tisotumab vedotin will not be dispensed in child-resistant packaging.

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.

For further details on packaging and labeling of tisotumab vedotin, please refer to the Pharmacy Binder.

5.3.6 Preparation

The dose of tisotumab vedotin for administration must be prepared by the trial site pharmacy using aseptic technique. The reconstituted tisotumab vedotin must be diluted into a 0.9% NaCl infusion bag containing 100mL according to the dose calculated for the patient.

The infusion must be completed within 24 hours after the tisotumab vedotin vials have been reconstituted. A 0.2 μm in-line filter must be used for the infusion. The entire (100 mL or

greater) infusion volume from the prepared infusion bag needs to be administered; no dead volume is provided.

Detailed drug preparation instructions are provided in the Pharmacy Binder.

5.4 Required Ocular Premedication and Preventive Eye Therapy

In order to prevent ocular AEs, all patients must adhere to ocular premedication and preventive eye therapy guidelines listed below (see also Appendix C):

- 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 sponsor's medical monitor.
- Use of eye cooling pads during infusion, e.g., Cardinal Health cold packs, refrigerator-based THERA PEARL Eye Mask, or similar. To be applied 5 minutes prior to start of infusion in accordance with the instructions provided with the eye cooling pads. The cooling pads must remain on the patient's eyes during the entire 30-60 minute infusion and for as long as 30 minutes afterwards.
- Application of steroid eye drops (dexamethasone 0.1% eye drops or equivalent) before and after each infusion for a total of 4 days. The first drops are to be given 24 hours prior to start of infusion. Continue treatment for 72 hours thereafter. Steroid eye drops should be administered as 1 drop in each eye, 3 times daily, or used in accordance with the product prescribing information.
- Use of lubricating eye drops during the whole treatment phase of the trial (i.e., from first dose of study drug until 30 days after the last dose of study drug). Frequent use of lubricating eye drops as per standard of care for patients receiving chemotherapy is recommended. Lubricating eyedrops should be self-administered daily or as needed according to the package insert or prescribed instructions from the ophthalmologist.
- It is recommended that patients not wear contact lenses while being treated with tisotumab vedotin from the first dose until 30 days after the last dose of study drug.

5.5 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent. Exceptions to this include medications administered for ocular AEs, which must be documented until resolution of the AE, return to baseline, or study closure, whichever comes first.

5.5.1 Required Concomitant Therapy

Please see Section 5.4 and Appendix C for required ocular premedication and preventive eye therapy schedule.

5.5.2 Allowed Concomitant Therapy

Use of the DigniCap Scalp Cooling System or other, similar scalp-cooling device according to guidelines is permitted to prevent alopecia if available at the clinical study site.

Anti-coagulation therapy for prophylaxis/treatment of thrombotic conditions is permitted with the following restrictions:

- A patient on anticoagulants when entering the study must be on a steady dose at least 4 weeks prior to study drug administration and must have INR and aPTT monitored prior to dosing. Patients on anticoagulation therapy requiring monitoring of the PT/INR should have their doses adjusted to target an INR ≤2.5 ULN at least 4 weeks prior to study drug administration. Coagulation parameters including fibrinogen, aPTT, PT, and INR must be measured locally prior to each dose of study drug as specified in Section 7.7.2.
- If a patient develops a new DVT/PE and requires initiation of therapeutic anticoagulation, therapy with tisotumab vedotin will be held until new anticoagulation has been started, and:
    - For vitamin K antagonists, patient must have been on a steady dose for at least 2 weeks with INR <2.5. Parenteral low molecular weight heparin (LMWH) must no longer be required for bridging.
    - For other anticoagulant agents that require additional parenteral agents during initiation, the parenteral agent must have been discontinued, and the anticoagulant must be on a steady dose for at least 2 weeks. (for e.g., edoxaban for new DVT/PE events, which can be started after an initial 5–10 days of parenteral anticoagulant as per the product label).
    - For agents that require a higher dose during initiation, (e.g., apixaban that is started at 10 mg orally twice per day, and then maintained at 5 mg twice per day), tisotumab vedotin will be held during initiation and can be resumed after 2 weeks on the stable maintenance dose.
    - For agents such as LMWH that are administered via weight-based dosing, tisotumab vedotin will be held during the initial 2 weeks of the introduction of new anticoagulant.
- Chronic use of antiplatelet therapy (ASA [aspirin], clopidogrel, and similar medications), as required for vascular diseases such as coronary artery disease, cerebrovascular accident, and similar conditions, is permitted on this study.

- A patient cannot receive both anticoagulant(s) and antiplatelet agent(s) concurrently while on study.

Each patient should be told to notify the trial site about any new medications they are taking after receiving the first tisotumab vedotin administration. All medications (other than tisotumab vedotin) and significant non-drug therapies (including herbal/natural medications, and blood transfusions) administered during the trial must be recorded in the eCRF.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as prohibited (Section 5.5.3). Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dates of administration and reasons for use.

5.5.3 Prohibited Concomitant Therapy

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

The following is prohibited:

- Curative intent radiation therapy, from the time of consent until the patient completes the trial, with the following exceptions:
    - Radiation therapy of a solitary non-target lesion IS allowed.
    - Palliative radiotherapy IS allowed as per RECIST criteria.
- Drugs and substances known to be strong CYP3A and/or P-gp inhibitors according to the US FDA's list of drug interactions should be avoided if possible. If administered, the patient must be closely observed for potential adverse reactions.

Patients may not receive other investigational drugs, immunosuppressive medications, or systemic anti-neoplastic therapy during the study.

5.6 Management of Adverse Reactions

5.6.1 Management of Infusion Reactions

IRRs may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. If anaphylaxis occurs, administration of tisotumab vedotin should be immediately and permanently discontinued.

All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRRs.

All patients should be observed for 2 hours after ending their first infusion of study drug and 15 minutes for all subsequent cycles. In case any clinically significant IRR is observed during or after the first infusion of study drug or at subsequent treatment cycles, the patient

should be observed for 2 hours after end of study drug administration for all following infusions.

For more information on infusion reactions, please refer to Section 5.3.2.

5.6.2 Management of Overdose

Weight-based dosing for tisotumab vedotin is based on the patient's actual body weight, with the exception of patients weighing greater than 100 kg. Dosing will be based on 100kg for these individuals. **The maximum dose permitted per infusion in this study is 90 mg or 120 mg for patients receiving the dose-dense regimen and 200 mg for patients receiving the Q3W regimen. If the dose for the dose-dense regimen is de-escalated to 0.65 mg/kg, the maximum dose permitted per infusion will be 65 mg.**

In the event of an overdose of tisotumab vedotin ≥10%, study personnel should:

- Care for and medically stabilize the patient until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of tisotumab vedotin.
- Consider growth factor support and monitoring of coagulation parameters with appropriate intervention as needed.
- Notify the sponsor's medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of tisotumab vedotin administered, patient weight) and adverse events, if any.

5.7 Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF. In addition, patients will be provided with a patient diary and instructed to record details of prophylactic eye drop usage each day.

6 STUDY ACTIVITIES

6.1 Schedule of Events

Adverse events and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.7.8). Any study protocol-related adverse event (defined in Section 7.7.8.1) as well as any concomitant medications given for treatment of the adverse event, should be recorded from the time of informed consent. A schedule of events is provided in Appendix A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

For all treatment cycles, clinical laboratory assessments (serum chemistry panel, complete blood count [CBC] with differential, coagulation parameters, and Hemoglobin Alc [HgbA1c]) as well as physical exam, weight, and ECOG performance status may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

Tumor biopsies performed outside protocol-specified time points during the study should be made available to the sponsor if feasible and if the patient has consented to submission of these samples (see Section 7.5.2). Biopsies performed at protocol-specified time points must be submitted to the sponsor.

Procedures listed below include only those that occur in the clinic or on the same day that a patient visits the clinic. See Appendix C for the preventative eye therapy schedule and dosing diary schedule. The PRO-CTCAE patient-reported outcomes questionnaire should be collected at baseline and weekly (±2 days) starting on Cycle 1 Day 1 through the end of treatment (Appendix A).

6.2 Screening Visit (Days [–28] to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Blood collection for CA-125 (results to be submitted to central laboratory)
- Medical history (see Section 7.1)
- Height and weight
- Physical exam
- Vital signs
- Eye exam performed by investigator (see Section 7.7.5 and Appendix C)
- Ophthalmologic evaluation performed by ophthalmologist (see Section 7.7.4)
- Electrocardiogram (ECG)
- Biopsy collection (See Section 7.1.1)
- Imaging

6.2.1 Baseline Visit (Days –7 to Day 1)

- Pregnancy test for patients of childbearing potential
- CBC with differential (results to be submitted to central laboratory)
- Chemistry panel (results to be submitted to central laboratory)
- Calculation of eGFR (See Section 7.7.2)
- Coagulation parameters (fibrinogen, INR, PT, and aPTT) (results to be submitted to central laboratory)
- HgbA1c (results to be submitted to central laboratory)
- ECOG performance status
- Parts A and B, US patients only: patient-reported outcomes questionnaires (all questions)

6.3 Treatment Period (Q3W Regimen only)

6.3.1 Day 1 (±1 day), All treatment cycles (exceptions noted)

- Cycle 1 only: Prior to dosing, confirm patient eligibility per inclusion/exclusion criteria
- Weight
- Physical Exam
- Predose vital signs
- ECOG Performance status (If Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Chemistry panel (results to be submitted to central laboratory; if Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- CBC with differential (results to be submitted to central laboratory; if Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Pregnancy test for patients of childbearing potential (If Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Coagulation parameters (fibrinogen, INR, PT, and aPTT) (results to be submitted to central laboratory; if Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Eye exam performed by investigator
- Predose blood sample for PK evaluation (within 24 hours) (Cycles 1, 2, 3, 4, 5, and every other cycle thereafter)
- Predose blood sample for antitherapeutic antibody (ATA) evaluation (within 24 hours) (Cycles 1, 2, 3, 4, 5, and every other cycle thereafter)
- Predose blood sample for plasma proteomic analysis (within 24 hours) (Cycles 1, 2, 3, 4, 5, and every other cycle thereafter)
- Predose blood sample for plasma mutational analysis (within 24 hours) (Cycles 1, 2, 3, 4, 5, and every other cycle thereafter)
- Predose blood sample for plasma exosome analysis (within 24 hours) (Cycles 1, 2, 3, 4, 5, and every other cycle thereafter)
- Predose blood sample for PBMC immune subsets analysis (within 24 hours) (Cycles 1, 2, 3, and 4 only)
- Ocular premedication and preventative eye therapy (see Section 5.4 and Appendix C)
- Ensure patient completes dosing diary
- Parts A and B, US patients only: Patient-reported outcomes questionnaires (all questions). If Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1.
- Tisotumab vedotin administration

- Blood samples for PK evaluation (all time points from end of infusion)
  - End of infusion (+ 15 minutes) (Cycles 1, 2, 3, 4, 5, and every other cycle thereafter)
  - 1 hour (±15 minutes) (Cycles 1 and 2 only)
  - 5 hours (±30 minutes) (Cycles 1 and 2 only)
- Blood samples for plasma proteomic analysis (all time points from end of infusion)
  - End of infusion (+15 minutes) (Cycles 1, 2, 3, 4, 5, and every other cycle thereafter)
  - 1 hour (±15 minutes) (Cycles 1 and 2 only)
  - 5 hours (±2 hours) (Cycles 1 and 2 only)

6.3.2 Cycle 1 and 2, Day 2

- Preventative eye therapy (see Section 5.4 and Appendix C)
- Ensure patient completes dosing diary

6.3.3 Cycle 1 and 2, Day 3

- Preventative eye therapy (see Section 5.4 and Appendix C)
- Blood sample for PK evaluation (48 hours ±4 hours after the end of infusion)
- Blood sample for plasma proteomic analysis (48 hours ±4 hours after the end of infusion)
- Ensure patient completes dosing diary

6.3.4 Cycle 1 Day 8 (±1 day)

- CBC with differential (results to be submitted to central laboratory)
- Chemistry panel (results to be submitted to central laboratory)
- Coagulation parameters (fibrinogen, INR, PT, and aPTT) (results to be submitted to central laboratory)
- Eye exam performed by investigator
- Blood sample for PK evaluation (168 hours ±24 hours after the end of infusion)
- Blood sample for plasma proteomic analysis (168 hours ±24 hours after the end of infusion)
- Parts A and B, US patients only: PRO-CTCAE patient-reported outcomes questionnaire

6.3.5 Cycle 1 and 2, Day 15

- Blood sample for PK evaluation (336 hours ±24 hours after the end of infusion)
- Blood sample for plasma proteomic analysis (336 hours ±24 hours after the end of infusion)
- Parts A and B, US patients only: PRO-CTCAE patient-reported outcomes questionnaire

6.3.6 Cycle 2, Day 8 (±1 day)

- Blood sample for PK evaluation (168 hours ±24 hours after the end of infusion)
- Blood sample for plasma proteomic analysis (168 hours ±24 hours after the end of infusion)
- Parts A and B, US patients only: PRO-CTCAE patient-reported outcomes questionnaire

6.4 Treatment Period (Dose-Dense Regimen only)

6.4.1 Day 1 (±1 day), All Treatment Cycles (Exceptions Noted)

- Cycle 1 only: Prior to dosing, confirm patient eligibility per inclusion/exclusion criteria
- Weight
- Physical Exam
- Predose vital signs
- ECOG Performance status (If Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Chemistry panel (results to be submitted to central laboratory; if Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- CBC with differential (results to be submitted to central laboratory; if Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Pregnancy test for patients of childbearing potential (If Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Coagulation parameters (fibrinogen, INR, PT, and aPTT) (results to be submitted to central laboratory; if Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1)
- Eye exam performed by investigator
- Predose blood sample for PK evaluation (within 24 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for ATA evaluation (within 24 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for plasma proteomic analysis (within 24 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for plasma mutational analysis (within 24 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for plasma exosome analysis (within 24 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for PBMC immune subsets analysis (within 24 hours) (Cycles 1, 2, 3, and 4 only)

- Ocular premedication and preventative eye therapy (see Section 5.4 and Appendix C)
- Ensure patient completes dosing diary
- Parts A and B, US patients only: patient-reported outcomes questionnaires (all questions). If Baseline Visit activities occur within 1 day prior, this assessment does not need to be repeated at Cycle 1, Day 1.
- Tisotumab vedotin administration
- Blood samples for PK evaluation (all time points from end of infusion)
  - End of infusion (+ 15 minutes) (Cycles 1, 2, 3, 4, 7 and every 3rd cycle thereafter)
  - 1 hour (±15 minutes) (Cycle 1 only)
  - 5 hours (±2 hours) (Cycle 1 only)
- Blood samples for plasma proteomic analysis (all time points from end of infusion)
  - 1 hour (±15 minutes) (Cycle 1 only)
  - 5 hours (±2 hours) (Cycle 1 only)

6.4.2 Cycles 1 and 2, Day 2

- Preventative eye therapy (see Section 5.4 and Appendix C)
- Ensure patient completes dosing diary

6.4.3 Cycles 1 and 2, Day 3

- Preventative eye therapy (see Section 5.4 and Appendix C)
- Blood sample for PK evaluation (48 hours ±4 hours after the end of infusion)
- Blood sample for plasma proteomic analysis (48 hours ±4 hours after the end of infusion)
- Ensure patient completes dosing diary

6.4.4 All Treatment Cycles, Day 8 (±1 day) (Exceptions Noted)

- Weight
- Physical Exam
- Predose vital signs
- Chemistry panel (results to be submitted to central laboratory)
- CBC with differential (results to be submitted to central laboratory)
- Coagulation parameters (fibrinogen, INR, PT, and aPTT) (results to be submitted to central laboratory)
- Eye exam performed by investigator
- Ocular premedication and preventative eye therapy (see Section 5.4 and Appendix C)
- Predose blood sample for PK evaluation (within 8 hours) (Cycles 1 and 2 only)
- Predose blood sample for plasma proteomic analysis (within 8 hours) (Cycles 1 and 2 only)
- Ensure patient completes dosing diary

- Parts A and B, US patients only: PRO-CTCAE patient-reported outcomes questionnaire
- Tisotumab vedotin administration

6.4.5 All Treatment Cycles, Day 15 (±1 day) (Exceptions Noted)

- Weight
- Physical Exam
- Predose vital signs
- Chemistry panel (results to be submitted to central laboratory)
- CBC with differential (results to be submitted to central laboratory)
- Coagulation parameters (fibrinogen, INR, PT, and aPTT) (results to be submitted to central laboratory)
- Eye exam performed by investigator
- Ocular premedication and preventative eye therapy (see Section 5.4 and Appendix C)
- Predose blood sample for PK evaluation (within 8 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for plasma proteomic analysis (within 8 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for plasma mutational analysis (within 8 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for plasma exosome analysis (within 8 hours) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
- Predose blood sample for PBMC immune subsets analysis (within 8 hours) (Cycles 1, 2, 3, and 4 only)
- Parts A and B, US patients only: PRO-CTCAE patient-reported outcomes questionnaire
- Ensure patient completes dosing diary
- Tisotumab vedotin administration
- Blood samples for PK evaluation (all time points from end of infusion)
  - End of infusion (within 15 minutes) (Cycles 1, 2, 3, 4, 7, and every 3rd cycle thereafter)
  - 1 hour (±15 minutes) (Cycle 1 only)
  - 5 hours (±2 hours) (Cycle 1 only)
- Blood samples for plasma proteomic analysis (all time points from end of infusion)
  - 1 hour (±15 minutes) (Cycle 1 only)
  - 5 hours (±2 hours) (Cycle 1 only)

6.4.6 Cycle 1, Day 17

- Blood sample for PK evaluation (48 hours ±4 hours after the end of infusion)

- Blood sample for plasma proteomic analysis (48 hours ±4 hours after the end of infusion)
- Preventative eye therapy (see Section 5.4 and Appendix C)

6.4.7 Cycle 1, Day 22 (±1 day)

- Blood sample for PK evaluation (168 hours ±24 hours after the end of infusion)
- Blood sample for plasma proteomic analysis (168 hours ±24 hours after the end of infusion)
- Parts A and B, US patients only: PRO-CTCAE patient-reported outcomes questionnaire (can be conducted remotely)

6.5 Response Assessments

Time points for radiographic exams should be calendar-based and do not depend on cycle visits. Imaging should be conducted on the following schedule until disease progression, start of a new cancer therapy, consent withdrawal, study termination by the sponsor, or death, whichever comes first:

- Every 6 weeks (±7 days) for 6 months after the first dose of tisotumab vedotin
- Every 12 weeks (±7 days) for the next 6 months (i.e., until 1 year after first dose)
- Every 6 months (±2 weeks) thereafter

Blood collections for CA-125 status should correspond as closely as possible with imaging visits (±5 days).

Responses must be evaluated with a confirmatory scan at least 4 weeks after initial response.

6.6 End of Treatment Visit (30 to 37 days after last dose of study drug)

End of Treatment (EOT) visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. Note: The time to EOT visit may be longer than 37 days. However, EOT evaluations must be performed before initiation of a new (non-protocol) therapy. If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted 30 to 37 days following the last treatment to assess for adverse events.

- Physical examination
- Vital signs
- Chemistry panel (results to be submitted to central laboratory)
- CBC with differential (results to be submitted to central laboratory)
- Pregnancy test for patients of childbearing potential
- Coagulation parameters (fibrinogen, INR, PT, and aPTT) (results to be submitted to central laboratory)
- HgbA1c (results to be submitted to central laboratory)

- Blood collection for CA-125 (results to be submitted to central laboratory; not required if conducted within 4 weeks prior to EOT)
- Eye exam performed by investigator
- ECOG performance status
- ECG
- Imaging (not required if conducted within 4 weeks prior to EOT)
- Subsequent anti-cancer therapy status
- Survival status
- Blood sample for PK evaluation
- Blood sample for ATA evaluation
- Blood sample for plasma proteomic analysis
- Blood sample for plasma mutational analysis
- Blood sample for plasma exosome analysis
- Blood sample for PBMC immune subsets analysis
- Parts A and B, US patients only: patient-reported outcomes questionnaires (both instruments)
- For patients discontinuing treatment due to disease progression: if a tumor biopsy was performed at the time of disease progression, submit sample of tumor specimen, if available and patient has signed consent to allow submission of this tissue (see Section 7.5.2)

6.7 Follow-up (Every 12 weeks ±1 week)

- Subsequent anti-cancer therapy status
- Survival status
- For patients of childbearing potential, a pregnancy test is to be performed 24 weeks after EOT (±7 days)

6.8 End of Study/End of Follow-up

The date the patient met criteria for study discontinuation and the reason for study discontinuation will be recorded.

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Only patients who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Patient medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

A physical exam, height and weight, vital signs, complete eye examination performed by the investigator, ophthalmologic exam by an ophthalmologist, eGFR, CT with contrast/MRI scan for baseline response efficacy assessment, biopsy collection, CA-125 blood collection, CBC with differential, serum chemistry panel, coagulation parameters including fibrinogen, INR, PT, and aPTT, HgbA1c, ECOG performance status, ECG, and pregnancy test (either urine or serum, for patients of childbearing potential) are required for all patients at screening and/or baseline as described in Section 6.2 and Appendix A.

7.1.1 Biopsy Collection

Fresh or archived biopsy tissue is required to be collected at baseline. Archived tumor tissue samples must have been obtained within 2 years prior to the first administration of tisotumab vedotin. Older specimens may be allowed upon approval of the sponsor's medical monitor. Fresh tissue must be obtained from a newly obtained core or excisional biopsy of a tumor lesion. If available, archived tumor tissue is also requested from patients who receive fresh biopsies. This will be used for additional biomarker analysis.

7.2 Response/Efficacy Assessments

The determination of antitumor activity will be based on objective response assessments made by the investigator according to the RECIST v1.1 (Eisenhauer 2009) and treatment decisions by the investigator will be based on these assessments. Clinical response of complete response (CR), partial response (PR), stable disease (SD), or PD will be determined at each assessment. In addition, images will be collected by an independent review facility for possible future analysis.

Measures of anti-cancer activity will be assessed by either CT with contrast or MRI scans at protocol-specified time points. **Patients must be evaluated using the same imaging method throughout the study for efficacy assessments.**

CT/MRI scans will include, at minimum, the chest, abdomen, and pelvis. Other regions should be scanned if the patient has known or suspected disease in that region.

Responses (CR or PR) will be confirmed with repeat scans at least 4 weeks after first documentation of response. The schedule for response assessments should not be adjusted after the confirmatory scan (e.g., CR at Week 6, confirmatory scans at Week 10, next assessment due at Week 12). Tumor imaging should also be performed whenever disease progression is suspected.

Patients who discontinue study treatment for reasons other than objective disease progression by RECIST v1.1 (see Appendix G) or subsequent cancer therapy will continue to receive CT/MRI scans every 6 weeks (±7 days) for the first 6 months after the first treatment with tisotumab vedotin (Cycle 1 Day 1). Between 6 and 12 months on study the frequency of response assessments will be reduced to every 12 weeks (±7 days). After 1 year on study, assessments will be reduced further to every 6 months (±2 weeks). Tumor assessments will continue until the patient has radiologically-confirmed disease progression per RECIST v1.1

by the investigator, initiates a new anti-cancer therapy, dies, withdraws consent, or the study closes, whichever comes first.

In patients who discontinue study treatment due to pregnancy, response assessments should be conducted as appropriate.

Patients' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

In addition to radiographic tumor assessments, expression level of CA-125 will also be monitored to assess response rate by CA-125 and the combination response of overall response/CA-125 as secondary endpoints. Blood collections for CA-125 should correspond as closely as possible with imaging visits (±5 days).

7.3 Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and ATA will be collected throughout the study per the sample collection schedule provided in Appendix B. Validated assays will be used to measure the concentrations of tisotumab vedotin and MMAE in serum or plasma. Two assays will be used for tisotumab vedotin: one detecting tisotumab vedotin only and one detecting total antibody. PK samples will be collected and archived for possible analysis of other tisotumab vedotin-related species. A qualified assay will be used to determine the levels of ATA in serum.

Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of samples. It may be possible to have some samples collected via home visits by an external home health aide vendor. More information regarding this service will be provided by the sponsor prior to the site initiation visit.

7.4 Patient-Reported Outcomes Assessments

Parts A and B, US patients only, validated instruments will be utilized for health-related quality of life assessment from the patient's perspective. Patients will be required to respond to questions related to physical functioning, adverse effects of treatment, and the overall burden of adverse effects. Patients will be requested to complete each of the questionnaires at timepoints described below before clinic visits (see Schedule of Events, Appendix A). Questionnaires may be completed remotely.

Each patient will have an option to answer questions electronically or via paper. Patients will respond to questions related to adverse effects (10 questions), the overall burden of adverse effects (1 question) and vision related problems (3 questions) every 7 days during a set time interval. Patients will respond to key physical functioning related questions (6 questions) on Day 1 of each treatment cycle before infusion of study drug and at the end of treatment visit (EOT).

The following instruments will be utilized:

- NCI PRO-CTCAE: Questions related to adverse effects patients may experience during the trial are taken from a set of items from the NCI PRO-CTCAE item bank. Of the 78 items related to symptomatic treatment toxicities available in NCI PRO-CTCAE, a total of 10 questions related to visual symptoms (blurred vision, watery eyes), gastrointestinal symptoms (nausea, vomiting, constipation, diarrhea, and abdominal pain) bleeding (bruising, nose bleeds), and neurological (numbness and tingling) were selected for this trial (see Appendix D).
- PROMIS (Patient-Reported Outcomes Measurement Information System): Patients will respond to 6 questions related to their ability to carry out various physical activities. The questions are from PROMIS (Patient-Reported Outcomes Measurement Information System) item bank (PROMIS Version 1.2 SF 6b–See Appendix D).

In addition to NCI PRO-CTCAE and PROMIS, 4 additional PRO questions have been added by the sponsor. Three of these questions allow patients to report symptoms related to color vision, near vision, and night vision, respectively, on a simple 5-point scale. (Appendix D). One additional question allows patient to report the overall effect of symptoms, also on a 5-point scale (Appendix D).

7.5 Biomarker Studies

Samples for exploratory biomarkers will be collected at protocol-specified time points per the schedule provided in Appendix B. Biomarker assessments will not be used for patient selection.

Methods of analysis may include immunohistochemistry (IHC), mIHF, Next Generation Sequencing, PCR, mutation and gene expression profiling; T-cell receptor beta chain sequencing, flow cytometry, and proteomic methodologies such as enzyme-linked immunosorbent assay (ELISA) and microvesicle assessment.

7.5.1 Protein Markers in Blood

The primary effects of tisotumab vedotin on tumor cells may lead to changes in the activation state of local, tumor-associated, and peripheral immune cells. Biomarker assessments in blood samples may include but may not be limited to CA-125 status and markers of immune function, including abundance and phenotype of immune cell subsets and abundance of cytokines. These may provide insight into treatment-related changes in activation state of peripheral immune system associated with tisotumab vedotin-induced tumor cell death.

7.5.2 Characterization of Tumor Tissue

To better understand relationships between pre-treatment tumor biological characteristics and patient outcome, submission of tumor tissue is required during the screening period (pretreatment). Patient is required to provide fresh tissue from a newly-obtained core or excisional biopsy of a tumor lesion OR an archived specimen obtained within 2 years of the

first administration of tisotumab vedotin. Older specimens may be allowed upon approval of the sponsor's medical monitor. Please see the Laboratory Manual for details.

Biomarker assessments in tumor tissue may include, but not be limited to:

- Tumor expression of TF protein
- Messenger ribonucleic acid (mRNA) expression (e.g., TF)
- Markers of disease subtype (e.g., The Cancer Genome Atlas [TCGA] subtypes)
- Mutational load
- Markers of the tumor immune microenvironment (e.g., PD-L1, CD4, CD8)

If available and the patient consents, archived tumor tissue is also requested from patients who received fresh biopsies. This tissue will be used for biomarker analysis.

Any unscheduled tumor biopsies performed while a patient is on study should be made available to the sponsor if feasible and if the patient has signed the consent form to allow submission of this tissue. For example, if a biopsy on residual tumor is performed at the end of treatment or at progression, a sample will be collected (if available).

7.6 Biospecimen Repository

In the US only, for patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.7 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including serious adverse events (SAEs), recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests. Safety assessments will be performed at prespecified time points through the end of treatment visit.

Safety will be monitored over the course of the study by an SMC which includes sponsor representatives including the study statistician, drug safety representative, and medical monitor as well as all investigators with at least one patient enrolled in the trial. An ongoing, real-time review of patient safety and SAEs will also be conducted by the sponsor's Drug Safety Department.

7.7.1 Vital Signs

Vital signs measures are to include heart rate, blood pressure (while patient is in seated position), and temperature.

7.7.2 Clinical Laboratory Tests

All clinical laboratory tests will be performed locally. This testing will include institutional standard tests for evaluating safety and making clinical decisions. With the exception of pregnancy testing, results of clinical laboratory tests are to be submitted to the central laboratory.

The following laboratory assessment(s) will be performed at scheduled time points (see Appendix A) during the course of the study:

- The estimated GFR (eGFR) should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL:

  eGFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

  If Scr is reported in µmol/L, the value should be converted to mg/dL using the conversion factor 0.011312 µmol/L to mg/dL.

- Coagulation parameters: fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
- A serum or urine β-hCG pregnancy test for patients of childbearing potential (See Section 7.7.6)
- Chemistry panel: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, LDH, phosphorus, potassium, sodium, glucose, gamma-glutamyl transferase (GGT), amylase, lipase, uric acid, and total bilirubin.
- CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- Hemoglobin Alc
- CA-125 expression levels

Test results for biochemistry, hematology, and coagulation factors must be obtained and reviewed by the investigator within 24 hours prior to trial treatment administration. Laboratory test values should be recorded in the eCRF if they are of clinical importance, e.g., used as supportive information on an AE or lead to dose modifications/delays of the trial treatment.

7.7.3 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Measurements of height obtained within the prior 12 months may be utilized.

7.7.4 Ophthalmological Exam

An ophthalmological evaluation must be performed by an ophthalmologist at screening prior to treatment with tisotumab vedotin. This screening exam will allow the ophthalmologist to have a pre-treatment assessment for adequate on-treatment comparison. In addition, patients must be referred for additional ophthalmological examinations if ocular symptoms occur or in the case of objective findings from scheduled eye exams at the site (see Section 5.3.1). Relevant physical findings from the ophthalmological examination must be documented in the eCRF (See Section 5.3.1). Assessments to be performed with results recorded on the eCRF include visual acuity, Schirmer's test, slit lamp, inspections of the conjunctivas and corneas including staining, intraocular pressure, and fundoscopy.

7.7.5 Eye Examination

Eye examination should be assessed by the investigator and should include a visual inspection of the eye orbit and conjunctiva and control of normal eye movement. The patient should be asked about any ocular symptoms (e.g., itchy eyes, sticky eyelids, eye secretion, blurry vision etc.).

In case of either subjective ocular symptoms and/or objective findings, every effort must be made to refer the patient to an ophthalmologist for prompt review within 3 days. Relevant physical findings from the ophthalmological examination must be documented in the eCRF (See Section 5.3.1).

7.7.6 Pregnancy Testing

For patients of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed locally at baseline, within 7 days prior to Day 1 of Cycle 1 and Day 1 of each subsequent cycle, and at the EOT visit.

A negative pregnancy result is required before the patient may receive each infusion of study drug. Pregnancy tests may also be repeated as requested per IRB/IEC or if required by local regulations.

7.7.7 Electrocardiogram

ECGs are to be obtained per institutional standard at time points defined in Section 6 and Appendix A. Routine 12-lead ECGs will be performed after the patient has been in a supine position for at least 5 minutes. Paper copies of the tracings will be used for data entry into the CRF.

7.7.8 Adverse Events

7.7.8.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded (i.e., hypertension).
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (predose, during and postdose) through the end of the safety reporting period (see Section 7.7.8.5). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.7.8.1 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE v5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to study treatment (tisotumab vedotin) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

Investigator and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

7.7.8.2 Procedures for Eliciting and Recording Adverse Events

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For IRRs, do not use the NCI CTCAE terms of “cytokine release syndrome,”

"acute infusion reaction," or "allergic or hypersensitivity reaction." Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease" or "Malignant Disease Progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s). Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF

All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.7.8.1) should be reported as SAEs.

Potential Drug-Induced Liver Injury

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Reuben 2004). Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential hepatotoxicity in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe drug-induced liver injury (DILI).

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (i.e., elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as a suspected unexpected serious adverse reaction (SUSAR) associated with the use of the drug and reported promptly to the sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity.

7.7.8.3 Reporting Periods for Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment (tisotumab vedotin), whichever is later.

However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the patient dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest (i.e., all ocular events) will be followed until resolution, return to baseline, or study closure.

7.7.8.4 Serious Adverse Events and AESIs Requiring Immediate Reporting

Within 24 hours of observing or learning of any SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen. Additionally, all ocular AEs (any grade, whether they meet seriousness criteria or not) must be reported to the sponsor within 24 hours. Ocular AEs are the only non-serious events that should be reported on an SAE form.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Patient number
- Date of event onset
- Description of the event
- Study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form) unless otherwise instructed on the sponsor's SAE form.

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.7.8.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.7.8.4). Investigators must also report all ocular AEs, whether or not they meet seriousness criteria, to the sponsor.

The sponsor will report all SAEs and ocular AEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity, as well as other SAEs that are not study endpoints but are known consequences of the underlying disease or condition that are anticipated to occur in the study population, should not be reported to the FDA as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Assessment for IND Safety Reporting Guidance for Industry (draft guidance December 2015).

In this study, progression of underlying malignancy is not reported as an AE or SAE. No individual IND safety reports will be submitted for progression of underlying malignancy. Progression of underlying malignancy will be evaluated as an efficacy endpoint.

7.8 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Response will be assessed according to RECIST v1.1, which are standardized criteria for evaluating response in the solid tumors comprising the cohorts in this study. The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to tisotumab vedotin. Pharmacokinetic assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of patients at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration, and withdrawal processes
- Current Investigator's Brochure
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good Clinical Practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing. and record keeping
- Patient coding
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study patients, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Seattle Genetics or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The CRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5 Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seattle Genetics.

9 DATA ANALYSIS METHODS

9.1 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%)

9.2 Study Endpoint Definitions

9.2.1 Confirmed ORR

Confirmed ORR is defined as the proportion of patients who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator. Patients who do not have at least 2 post-baseline response assessments (initial response and confirmation scan) will be counted as non-responders.

9.2.2 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.

9.2.3 CA-125 Response Rate

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 absolute value of the confirmatory sample must be ≤110% of the prior sample. Only patients who have an elevated baseline CA-125 value of ≥2 x ULN and within 2 weeks prior to the first dose of study drug will be included in the analysis.

9.2.4 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). The combined overall response will be assessed as indicated in Table 8.

Table 8: 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.

9.2.5 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients who achieve a 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 will be counted as non-responders.

9.2.6 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 started a new anti-cancer 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 progressed or died after an extended loss to follow up (i.e., ≥2 consecutive missed disease assessments) will be censored at the date of the last disease 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.

9.2.7 Time to Response

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). TTR will only be calculated for patients who achieve a confirmed CR or PR, and will be summarized with descriptive statistics.

9.2.8 Progression-Free Survival

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 9.2.6 for DOR will be applied to PFS. Patients who are not known to have died and who do not have an evaluation of tumor response after their first dose of study drug will be censored at Day 1.

9.2.9 Overall Survival

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).

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

Patients enrolled in the safety run-in portion, Part A and Part B will be summarized separately. All analyses in Part A and Part B will be presented by cohort and total 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.

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

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).

9.3.1.1 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.

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

9.3.1.2 Adjustments for Covariates

No adjustments for covariates are planned in the analyses.

9.3.1.3 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. Missing subsequent anti-cancer treatment start date will be imputed while deriving the time-to-event endpoints as applicable. Censoring rules will be applied for the analysis of time-to-event endpoints. Details will be provided in the SAP.

9.3.1.4 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.

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned in this study.

9.3.1.6 Data Transformations and Derivations

Time variables based on 2 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.

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

9.3.1.7 Analysis Sets

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

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.

The DLT evaluable analysis set includes all patients who received any amount of study drug and have completed the DLT evaluation period or have experienced a DLT. The DLT evaluable set applies only to the safety run-in cohort.

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 discontinued from the study or started subsequent cancer therapy. The EE analysis set will be used for supplemental analysis of efficacy endpoints as applicable.

The CA-125 evaluable analysis set includes patients with ovarian cancer who have an elevated baseline CA-125 value of ≥2 x ULN and 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.

9.3.1.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroups may include but are not limited to the following:

- Platinum-free interval
- Histology
- First line vs. second line PROC
- TF expression
- Prior treatment with CPIs
- Prior treatment with PARP inhibitors

9.3.1.9 Timing of Analyses

The primary analysis of study will be conducted when all treated patients have been followed for at least 6 months or come off study, whichever comes first. 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.

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

9.3.2 Patient Disposition

An accounting of study patients by disposition will be tabulated and the number of patients in each analysis set will be summarized. Patients who discontinue study treatment and patients who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3 Patient Characteristics

Demographics and other baseline characteristics will be summarized for the FAS. Details will be provided in the SAP.

9.3.4 Efficacy Analyses

The primary analysis of efficacy endpoints will be based on the FAS unless otherwise specified. Supplemental analysis of efficacy endpoints may be performed using the EE analysis set.

9.3.4.1 Primary Efficacy Analyses

The primary endpoint of this study is the confirmed ORR according to RECIST v1.1 per investigator assessment. The ORR is defined as the proportion of patients who achieve a confirmed CR or PR. The confirmed ORR and its exact 2-sided 95% CI will be calculated.

9.3.4.2 Secondary Efficacy Analyses

The confirmed and unconfirmed ORR according to RECIST v1.1, CA-125 response rate, and combined RECIST/CA-125 overall response rate will be estimated and the 95% CIs will be calculated. In addition, the TTR will be summarized for patients who achieve confirmed objective responses.

The DOR, PFS, and OS will be estimated using the Kaplan-Meier methodology and the medians and associated 95% CIs will be calculated. Kaplan-Meier plots will be provided as appropriate. The 6 month PFS rate and the 6 month OS rate will be estimated with 95% CI.

9.3.5 Pharmacokinetic and Immunogenicity Analyses

Tisotumab vedotin and MMAE concentrations will be summarized with descriptive statistics at each PK sampling time point. Selected PK parameters for tisotumab vedotin and MMAE will be estimated by noncompartmental analysis and summarized using descriptive statistics. These data may be combined with PK data from other clinical trials with tisotumab vedotin for population PK and PK/pharmacodynamic analyses.

The incidence of ATA will be summarized using the safety analysis set.

9.3.6 Biomarker Analyses

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.

9.3.7 Patient-Reported Outcomes Analyses

Patient-reported outcomes from Parts A and B US patients will be summarized over time with descriptive statistics by visit, using the FAS. Details will be provided in the SAP.

9.3.8 Safety Analyses

All safety analyses will be performed using the safety analysis set.

9.3.8.1 Extent of Exposure

Extent of exposure will be summarized by cohort for the safety analysis set. Summary statistics for duration of therapy, number of cycles, total dose, and dose intensity will be presented. Dose modifications, including dose delay, dose reduction, and unplanned dose adjustment, will be summarized. Details will be provided in the SAP.

9.3.8.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher treatment-emergent AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. Adverse events will be defined as treatment emergent if they are newly occurring or worsen after first dose of study treatment and including 30 days after last dose of study treatment.

Treatment-emergent AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 patient, the AE will be counted only once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AESIs and AEs leading to premature discontinuation of study drug will also be summarized and listed in the same manner.

9.3.8.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.8.4 Clinical Laboratory Results

Summary statistics of laboratory results and changes from baseline will be tabulated by scheduled visit. Grading of laboratory values will be assigned programmatically per the NCI CTCAE v5.0. Shift tables comparing the worst post-baseline to baseline CTCAE grade will be presented. Laboratory values will be listed with grade per CTCAE and flagged when values are outside the normal reference range.

9.3.8.5 Other Safety Analyses

Vital Signs

Vital signs data will be listed. Summary statistics of vital signs and change from baseline may be tabulated where appropriate.

ECOG Status

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

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.

9.3.9 Interim Analyses

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. A SMC consisting of the investigators, study medical monitor, biostatistician, and drug safety representative will review the data before proceeding to Part A.

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 determine 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 9 summarizes the PPoS based on the number of responses observed among the first 20 patients. Details of the calculation of PPoS are shown in Appendix I.

Table 9: 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 10. 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 10: 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.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 [R2]; FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the patient in simple terms using the IRB/IEC approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each patient, or legally authorized representative, if applicable to this study, by

obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally authorized representative for a patient who is unable to provide informed consent at study entry (if applicable), but the patient is later able to provide informed consent, the investigator must obtain written informed consent from the patient.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for

enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4 Study Documentation, Privacy, and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of patient identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5 Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS

SCHEDULE OF EVENTS: Q3W REGIMEN

		Screening/Baseline		Every 21-day cycle	Cycle 1 only			EOT	F/U
	Day	D –28 to 1	D –7 to 1	D1[A]	D2	D3	D8	Within 30–37D of last dose[B]	Every 12 wks[C]
	Visit window			±1d			±1d		±7d
Screening/ Baseline Assessments	Informed consent	X							
	Inclusion/Exclusion criteria	X							
Safety Assessments	Physical exam	X		X[F]				X	
	Medical history	X							
	Height and weight	X		X[D]					
	Vital signs	X		X				X	
	CBC with differential[E]		X	X[F]			X	X	
	Chemistry panel[E]		X	X[F]			X	X	
	eGFR		X						
	Coagulation parameters[E]		X	X[F]			X	X	
	Pregnancy test (patients of childbearing potential)[G]		X	X[F]				X	X[H]
	HgbA1c[E]		X					X	
	Ocular Safety Measures	**See schedules in** Appendix C							
	ECOG performance status		X	X[F]				X	
	ECG	X						X	
	Concomitant medications	Related to study procedures[I]		Collect from Day 1 predose through safety reporting period					
	Adverse event collection								
Treatment	Study drug administration			X					
PK/ATA/ Biomarker Samples	Biopsy collection	X							
	Blood/tissue sample collection	**See schedules in Appendix B and Appendix C**							
Response Assessment	Imaging	X		Every 6 weeks[J]				X[K]	X[J, N]
	CA-125 blood collection	X		Every 6 weeks[L]				X[K]	
Parts A and B US only: Patient-Reported Outcomes: PROMIS[M]	Questionnaires		X	X[F]				X	
Parts A and B US only: Patient-Reported Outcomes: PRO-CTCAE[M]	Questionnaires		X	To be collected weekly ±2 days, starting on C1D1 and continuing weekly through EOT[F]					
Subsequent Anti-Cancer Therapy Status								X	X
Survival Status								X	X

A Day 1 of cycle 1 is to be performed no more than 28 days after the screening visit. Day 1 of cycle 2 is to be performed 21 days ±3 days after Day 1 of cycle 1, Day 1 of cycle 3 is to be performed 21 days ±1 days after Day 1 of cycle 2 etc.

B EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred.

C A telephone call should be performed in order to collect information of survival and new anti-cancer treatment as specified in Section 6.7.

D Height measurement needed at screening visit only.

E Clinical laboratory testing is to be performed locally. With the exception of pregnancy testing, results are to be submitted to the central laboratory.

F If this assessment occurs within 1 day prior to Cycle 1, Day 1, it does not need to be repeated at Visit 1.

G Only for patients of childbearing potential (please refer to Section 4 3 for definition). Serum or urine (beta-hCG) laboratory test with minimum sensitivity level of 25 mIU/mL must be taken at Baseline. A pregnancy test must be taken every cycle, (i.e., on Day 1), and at the EOT visit.

H A single follow-up pregnancy test is to be performed at 24 weeks (±7 days) after EOT.

I From time of informed consent.

J CT or MRI scans must be performed every 6 weeks (±7 days) for 6 months after the first study drug administration (regardless of study drug administration delays) and every 12 weeks (±7 days) for the next 6 months (regardless of study drug administration delays) and every 6 months (±2 weeks) thereafter. Responses must be evaluated with a confirmatory scan at least 4 weeks after initial response. Scans are to be performed until disease progression, start of new anti-cancer therapy, study termination, or death. Time points for radiographic exams should be calendar based and do not depend on cycle visits. CT of chest/abdomen/pelvis.

K Not required if conducted within 4 weeks prior to EOT.

L Blood collection for CA-125 should coincide with imaging visits (see timeline in footnote K) as closely as possible (±5 days). Collected locally. Results are to be submitted to the central laboratory.

M Parts A and B US patients only. To be collected before clinic visits, when applicable. Can be collected remotely.

N Collect blood samples for CA-125 at the time of CT or MRI scans.

SCHEDULE OF EVENTS: DOSE-DENSE REGIMEN

		Screening/Baseline		Every 28-day cycle			EOT	F/U
	Day	D –28 to 1	D –7 to 1	D1[A]	D8	D15	Within 30–37D of last dose[B]	Every 12 wks[C]
	Visit window			±1d	±1d	±1d		±7d
Screening/ Baseline Assessments	Informed consent	X						
	Inclusion/Exclusion criteria	X						
Safety Assessments	Physical exam	X		X[F]	X	X	X	
	Medical history	X						
	Height and weight	X		X[D]	X[D]	X[D]		
	Vital signs	X		X	X	X	X	
	CBC with differential[E]		X	X[F]	X	X	X	
	Chemistry panel[E]		X	X[F]	X	X	X	
	eGFR		X					
	Coagulation parameters[E]		X	X[F]	X	X	X	
	Pregnancy test (patients of childbearing potential)[G]		X	X[F]			X	X[H]
	HgbA1c[E]		X				X	
	Ocular Safety Measures	**See schedules in Appendix C**						
	ECOG performance status		X	X[F]			X	
	ECG	X					X	
	Concomitant medications	Related to study procedures[I]		Collect from Day 1 predose through safety reporting period				
	Adverse event collection							
Treatment	Study drug administration			X	X	X		
PK/ATA/ Biomarker Samples	Biopsy collection	X						
	Blood/tissue sample collection	**See schedules in Appendix B and Appendix C**						
Response Assessment	Imaging	X	Every 6 weeks[J]				X[K]	X[J, N]
	CA-125 blood collection	X	Every 6 weeks[L]				X[K]	
Parts A and B US only: Patient-Reported Outcomes: PROMIS[M]	Questionnaires		X	X[F]			X	
Parts A and B US only: Patient-Reported Outcomes: PRO-CTCAE[M]	Questionnaires		X	To be collected weekly ±2 days, starting on C1D1 and continuing weekly through EOT[F]				
Subsequent Anti-Cancer Therapy Status							X	X
Survival Status							X	X

A Day 1 of cycle 1 is to be performed no more than 28 days after the screening visit. Day 1 of cycle 2 is to be performed 28 days ±3 days after Day 1 of cycle 1, Day 1 of cycle 3 is to be performed 28 days ±1 days after Day 1 of cycle 2 etc.

B EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred.

C A telephone call should be performed in order to collect information of survival and new anti-cancer treatment as specified in Section 6.7.

D Height measurement needed at screening visit only.

E Clinical laboratory testing is to be performed locally. With the exception of pregnancy testing, results are to be submitted to the central laboratory.

F If this assessment occurs within 1 day prior to Cycle 1, Day 1, it does not need to be repeated at Visit 1.

G Only for patients of childbearing potential (please refer to Section 4.3 for definition). Serum or urine (beta-hCG) laboratory test with minimum sensitivity level of 25 mIU/mL must be taken at Baseline. A pregnancy test must be taken every cycle, (i.e., on Day 1), and at the EOT visit.

H A single follow-up pregnancy test is to be performed at 24 weeks (±7 days) after EOT.

I From time of informed consent.

J CT or MRI scans must be performed every 6 weeks (±7 days) for 6 months after the first study drug administration (regardless of study drug administration delays) and every 12 weeks (±7 days) for the next 6 months (regardless of study drug administration delays) and every 6 months (±2 weeks) thereafter. Responses must be evaluated with a confirmatory scan at least 4 weeks after initial response. Scans are to be performed until disease progression, start of new anti-cancer therapy, study termination, or death. Time points for radiographic exams should be calendar based and do not depend on cycle visits. CT of chest/abdomen/pelvis.

K Not required if conducted within 4 weeks prior to EOT.

L Blood collection for CA-125 should coincide with imaging visits (see timeline in footnote K) as closely as possible (±5 days). Collected locally. Results are to be submitted to the central laboratory.

M Parts A and B US patients only. To be collected before clinic visits, when applicable. Can be collected remotely.

N Collect blood samples for CA-125 at the time of CT or MRI scans.

APPENDIX B: PK, ATA, AND BIOMARKER SAMPLING TIME POINTS

Q3W REGIMEN

Cycle	Study Day	Time	Window	Relative Time	TV PK	TV ATA	Plasma proteomic	Plasma mutational analysis	Plasma exosome	PBMC immune subsets	Biopsy Collection
Screening	Day –28 to –1	N/A	N/A	N/A							X[A]
1 and 2	1	Predose	Within 24 hr	TV infusion start	X	X	X	X	X	X	
		End of infusion	+ 15 min	TV infusion end	X		X				
		1 hr	±15 min	TV infusion end	X		X				
		5 hr	±2 hr	TV infusion end	X		X				
	3	48 hr	±4 hr	TV infusion end	X		X				
	8	168 hr	±24 hr	TV infusion end	X		X				
	15	336 hr	±24 hr	TV infusion end	X		X				
3 and 4	1	Predose	Within 24 hr	TV infusion start	X	X	X	X	X	X	
		End of infusion	+15 min	TV infusion end	X		X				
5 and every other cycle thereafter	1	Predose	Within 24 hr	TV infusion start	X	X	X	X	X		
		End of infusion	+15 min	TV infusion end	X		X				
EOT					X	X	X	X	X	X	
Unscheduled											X[B]

A Fresh or archived biopsy tissue is to be collected at baseline. Archived tumor tissue samples must have been obtained within 2 years prior to the first administration of tisotumab vedotin. Older specimens may be allowed upon approval of the sponsor's medical monitor. Fresh tissue must be obtained from a newly obtained core or excisional biopsy of a tumor lesion.

B Unscheduled tumor biopsies performed while the patient is on study should be made available to the sponsor if feasible and if patient consents to the submission of this tissue. For example, if a biopsy on residual tumor is performed at the end of treatment or at progression, a sample will be collected (if available).

DOSE-DENSE REGIMEN

Cycle	Dose	Study Day	Time	Window	Relative Time	TV PK	TV ATA	Plasma Proteomic	Plasma mutational analysis	Plasma exosome	PBMC immune subsets	Biopsy Collection
Screening	N/A	Day –28 to –1	N/A	N/A	N/A							X[A]
1	1	1 (Dose No.1)	Predose 1	Within 24 hr	TV infusion start	X	X	X	X	X	X	
			End of infusion 1	+ 15 min	TV infusion end	X						
			1 hr	±15 min	TV infusion end	X		X				
			5 hr	±2 hr	TV infusion end	X		X				
		3	48 hr	±4 hr	TV infusion end	X		X				
	2	8 (Dose No.2)	Predose 2	Within 8 hr	TV infusion start	X		X				
	3	15 (Dose No.3)	Predose 3	Within 8 hr	TV infusion start	X		X	X	X	X	
			End of infusion 3[B]	Within 15 min	TV infusion end	X						
			1 hr[B]	±15 min	TV infusion end	X		X				
			5 hr[B,]	±2 hr	TV infusion end	X		X				
		17	48 hr[B]	±4 hr	TV infusion end	X		X				
		22	168 hr	±24 hr	TV infusion end	X		X				
2	1	1 (Dose No.1)	Predose 1	Within 24 hr	TV infusion start	X	X	X	X	X	X	
			End of infusion 1	Within 15 min	TV infusion end	X						
		3	48 hr	±4 hr	TV infusion end	X		X				
	2	8 (Dose No.2)	Predose 2	Within 8 hr	TV infusion start	X		X				
	3	15 (Dose No. 3)	Predose 3	Within 8 hr	TV infusion start	X		X	X	X	X	
			End of infusion 3[B]	Within 15 min	TV infusion end	X						
3 and 4	1	1 (Dose No.1)	Predose	Within 24 hr	TV infusion start	X	X	X	X	X	X	
			End of infusion	+15 min	TV infusion end	X						
	3	15 (Dose No.3)	Predose	Within 24 hr	TV infusion start	X						
			End of infusion	+15 min	TV infusion end	X						
7 and every 3rd cycle thereafter	1	1 (Dose No.1)	Predose	Within 24 hr	TV infusion start	X	X	X	X	X		
			End of infusion	+ 15 min	TV infusion end	X						
	3	15 (Dose No.3)	Predose	Within 24 hr	TV infusion start	X						
			End of infusion	+ 15 min	TV infusion end	X						
EOT						X	X	X	X	X	X	
Unscheduled												X[C]

A Fresh or archived biopsy tissue is to be collected at baseline. Archived tumor tissue samples must have been obtained within 2 years prior to the first administration of tisotumab vedotin. Older specimens may be allowed upon approval of the sponsor's medical monitor. Fresh tissue must be obtained from a newly obtained core or excisional biopsy of a tumor lesion.

B Do not collect samples at this timepoint if the patient is not administered tisotumab vedotin on D15 (see dose modifications in Section 5.2.3).

C Unscheduled tumor biopsies performed while the patient is on study should be made available to the sponsor if feasible and if patient consents to the submission of this tissue. For example, if a biopsy on residual tumor is performed at the end of treatment or at progression, a sample will be collected (if available).

APPENDIX C: OCULAR SAFETY MEASURES

Q3W REGIMEN: EVERY TREATMENT CYCLE

		Screening	Day –1	Day 1	Day 2	Day 3
Week 1	Ophthalmological Evaluation[A]	X				
	Eye exam	X		X		
	Cooling Eye Pads (start 5 min prior to infusion and apply 30–60 min)			X		
	Steroid Eye Drops (3x/day)[B]		X	X	X	X
	Vasoconstrictor Eye Drops			X		
	Lubricating Eye Drops (frequent use w/symptoms)[C]			X	X	X
	Patient diary entries	X		X	X	X
			Day 7	**Day 8**	**Day 9**	**Day 10**
Week 2	Eye exam			X[D]		
	Lubricating eye drops [C]		X	X	X	X
	Patient diary entries			X	X	X
				Day 15	**Day 16**	**Day 17**
Week 3	Lubricating eye drops (frequent use w/ symptoms) [C]			X	X	X
	Patient diary entries			X	X	X
						EOT
EOT	Eye exam					X

A Required ophthalmological evaluation performed by a local ophthalmologist at baseline. Patients experiencing ocular symptoms at any time on study must be referred to an ophthalmologist for prompt review (within 3 days), see Section 5 3.

B Steroid eye drops are to be administered 3 times daily on Days –1, 1, 2, and 3 of every treatment infusion. Drops should be administered during clinic visits on Day 1 of each cycle. See Section 5.4.

C To be self-administered daily or as needed according to the package insert or prescribed instructions from the ophthalmologist.

D Cycle 1 only.

DOSE-DENSE REGIMEN: EVERY TREATMENT CYCLE

		Screening	Day -1	Day 1	Day 2	Day 3
Week 1	Ophthalmological Evaluation[A]	X				
	Eye exam	X		X		
	Cooling Eye Pads (start 5 min prior to infusion and apply 30-60 min)			X		
	Steroid Eye Drops (3x/day)[B]		X	X	X	X
	Vasoconstrictor Eye Drops			X		
	Lubricating Eye Drops[C]			X	X	X
	Patient diary entries		X	X	X	X
			Day 7	**Day 8**	**Day 9**	**Day 10**
Week 2	Eye exam			X		
	Cooling Eye Mask (start 5 min prior to infusion)			X		
	Steroid Eye Drops (3x/day)[B]		X	X	X	X
	Vasoconstrictor Eye Drops			X		
	Lubricating Eye Drops[C]		X	X	X	X
	Patient diary entries		X	X	X	X
			Day 14	**Day 15**	**Day 16**	**Day 17**
Week 3	Eye exam			X		
	Cooling Eye Mask (start 5 min prior)			X		
	Steroid Eye Drops (3x/day) [B]		X	X	X	X
	Vasoconstrictor Eye Drops			X		
	Lubricating Eye Drops[C]		X	X	X	X
	Patient diary entries		X	X	X	X
				Day 22	**Day 23**	**Day 24**
Week 4	Lubricating Eye Drops[C]			X	X	X
	Patient diary entries			X	X	X
						EOT
EOT	Eye Exam					X

A Required ophthalmological evaluation performed by a local ophthalmologist at baseline. Patients experiencing ocular symptoms at any time on study must be referred to an ophthalmologist for prompt review (within 3 days), see Section 5 3.

B Steroid eye drops are to be administered 3 times daily on Days -1, 1, 2, and 3 of every treatment infusion. Drops should be administered during clinic visits for each infusion. See Section 5.4.

C To be self-administered daily or as needed according to the package insert or prescribed instructions from the ophthalmologist.

APPENDIX D: PATIENT-REPORTED OUTCOMES SURVEYS (PARTS A AND B US PATIENTS ONLY)

NCI PRO-CTCAE

Item Library Version 1.0

English

Form created on 06 July 2018

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an in the one box that best describes your experiences over the past 7 days.

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	o Never	o Rarely	o Occasionally	o Frequently	o Almost constantly
1a.	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
2.	In the last 7 days, how OFTEN did you have VOMITING?				
	o Never	o Rarely	o Occasionally	o Frequently	o Almost constantly
2a.	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
3.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	o Never	o Rarely	o Occasionally	o Frequently	o Almost constantly
5.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	o Never	o Rarely	o Occasionally	o Frequently	o Almost constantly
5a.	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe

5b.	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	o Not at all	o A little bit	o Somewhat	o Quite a bit	o Very much
6.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
6a.	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	o Not at all	o A little bit	o Somewhat	o Quite a bit	o Very much
7.	In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
7a.	In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
	o Not at all	o A little bit	o Somewhat	o Quite a bit	o Very much
8.	In the last 7 days, what was the SEVERITY of your WATERY EYES (TEARING) at their WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
8a.	In the last 7 days, how much did WATERY EYES (TEARING) INTERFERE with your usual or daily activities?				
	o Not at all	o A little bit	o Somewhat	o Quite a bit	o Very much
9.	In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?				
	o Yes		o No		
10.	In the last 7 days, how OFTEN did you have NOSEBLEEDS?				
	o Never	o Rarely	o Occasionally	o Frequently	o Almost constantly
10a.	In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
Do you have any other symptoms that you wish to report?					
o Yes			o No		

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	o None	o Mild	o Moderate	o Severe	o Very severe

Other questions to be asked weekly (same schedule as PRO-CTCAE questions):

1. I am bothered by the side effects of treatment:
   a. Not at all
   b. A little bit
   c. Somewhat
   d. Quite a bit
   e. Very much

2. How much difficulty do you have doing work or hobbies that require you to see well up close?
   a. No difficulty at all
   b. A little difficulty
   c. Moderate difficulty
   d. Extreme difficulty
   e. Stopped doing this because of your eyesight

3. Do you have difficulty seeing colors?
   a. No difficulty at all
   b. A little difficulty
   c. Moderate difficulty
   d. Extreme difficulty
   e. Stopped doing this because of your eyesight

4. How much difficulty do you have driving at night?
   a. No difficulty at all
   b. A little difficulty
   c. Moderate difficulty
   d. Extreme difficulty
   e. Stopped doing this because of your eyesight

Physical Function – Short Form 6b

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFC12	Does your health now limit you in doing two hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

APPENDIX E: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		Lansky		ECOG	
Percent	Description	Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, play activity.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet active play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.		
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.		
0	Dead.	0	Dead.	5	Dead.

APPENDIX F: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 6 months after the final dose of study drug; see Section **Error! Reference source not found.**).

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods (please see acceptable combinations below):

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Barrier method (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

b A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception).

Acceptable combinations of contraceptive methods:

- Hormonal method and barrier method
- Intrauterine device and barrier method
- Tubal ligation and barrier method

Unacceptable methods of contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms
- Barrier methods alone, including double-barrier methods

APPENDIX G: RECIST CRITERIA SUMMARY (VERSION 1.1)

Response Evaluation Criteria in Solid Tumors	
Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Measurable lesion	Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm).

From RECIST Version 1.1 (Eisenhauer 2009)

A response (CR or PR) will be considered confirmed if the following disease assessment (at least 4 weeks after the initial response) still shows response (CR or PR). In cases where the initial response is followed by SD, it will be considered as confirmed if the SD is later followed by PR or CR. For example, if a patient had PR in week 6, SD in Week 12, and PR in Week 18, this PR will be considered as confirmed.

APPENDIX H: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

On-line source: http://www heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX I: CALCULATION OF PREDICTIVE PROBABILITY OF SUCCESS

1. Let N_{max} be the maximum sample size of a cohort, and n be the number of patients treated and evaluated for the response status by the time of interim analysis

2. Assume the prior distribution of the response rate p follows a beta distribution

   $p \sim \text{beta}(a_0, b_0)$

Note: A weakly informative prior with a0 = 0.12 and b0 = 0.88 is chosen for this study to reflect the prior belief of 12% ORR with tisotumab vedotin, and let the data speak for itself so that inferences are not overly affected by information external to the observed data.

3. Let X be the number of responders in the first n patients, and X follows a binomial distribution

   $X \sim binomial(n, p)$

   The likelihood function for the observed data x is $L(p \mid X = x) \propto p^x (1- p)^{n - x}$

4. With the Bayes theorem, the posterior distribution of the response rate given $X = x$ follows a beta distribution

   $p \mid x \sim beta(a_0 + x, b_0 + n - x)$

5. Let Y be the number of responders in the potential m future patients, where $m = (N_{max} - n)$, thus Y follows a beta-binomial distribution

   $Y \sim \text{beta-binomial}(m, a0 + x, b0 + n - x)$

Given $Y = i$, the posterior distribution of p follows beta($a_0 + x + i, b_0 + N_{max} - x - i$)

6. Let $B_i = \Pr(p > p_0 \mid x, Y = i)$, where B_i measures the probability that the response rate p exceeds p_0 (the response rate of current stand of care), given x responders in the first n patients and i responders in the m future patients

7. Compare B_i to a threshold value θ_T. If $B_i > \theta_T$, then the cohort is considered "success" at the end of the cohort given the interim data and the potential outcome of $Y = i$.

Note: A more relaxed threshold value, $\theta_T = 70\%$, is chosen for this study given the exploratory nature of study.

$$PPoS = \sum_{i=0}^{m} \{\Pr(Y = i \mid x) \bullet I(\Pr(P > p_0 \mid x, Y = i) > \theta_T)\} = \sum_{i=0}^{m} \{\Pr(Y = i \mid x) \bullet I(B_i > \theta_T)\}$$

APPENDIX J: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol 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".

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX K: DOCUMENT HISTORY

Version	Date
Original	20 July 2018
Amendment 1	12 October 2018
Amendment 2	02 May 2019
Amendment 3	17 Oct 2019
Amendment 4	24 Aug 2020

SUMMARY OF CHANGES IN AMENDMENT 1

Section(s)	Change	Rationale
Title page	Changed version number and date	Administrative changes
Synopsis, 3.1	Changed description of DLTs and added safety data collection period	Clarification
	Revised text regarding preclinical experience with tisotumab vedotin	Aligned text to match updated Investigator's Brochure
1.3.2	More detail added to DLT criteria for bleeding; expanded scope of DLTs for ocular events	Clarification and alignment with other tisotumab vedotin protocols
	Specified in inclusion criterion 5 that measureable disease is defined as having lesion/s described in A) OR the lesion/s described in b), not both.	Clarification
3.1.1	Changed exclusion criterion 17 from "peripheral neuropathy > Grade 1" to "peripheral neuropathy ≥ Grade 2."	Alignment of language with other tisotumab vedotin protocols.
	Changes to required ocular premedication and preventive eye therapy	Alignment with other tisotumab vedotin protocols
4.1	Removal of "physical therapy" from list of non-drug therapies that must be recorded in the eCRF	Information regarding concomitant physical therapy is not necessary
	Visit windows (±1 day) added to Schedule of Events descriptions of several visits.	Alignment with Schedule of Events tables in Appendix A
4.2	Removed required on-treatment ophthalmological exam	Alignment with other tisotumab vedotin protocols
	Changed termination of patient-reported outcomes to end of treatment, not end of treatment or resolution of remaining AEs, whichever occurs later.	PRO data is not required after end of treatment.
5.4, Appendix C	Revisions to "minimum level for action" for specific individual symptoms on PRO surveys	Ease of implementation at clinical sites
	Added AESIs to section title	Clarification
5.5.2	Deleted a footnote describing the ePRO tools used	Footnote not necessary as each tool is already listed in its own row in the table
	Numbers added to some questions; one mistaken menu choice removed from Question 5	Clarification; correction

SUMMARY OF CHANGES IN AMENDMENT 2

Section(s)	Change	Rationale
Title page, Synopsis	Changed version number and date	Administrative changes
	Edited ">Grade 1" to read "≥ Grade 2"	Clarification to make text match between synopsis and Section 4.
Synopsis	Relaxation of biopsy requirements	Reduce barriers to enrollment.
	Specify that PRO questionnaires are only to be performed in Phase 2 US patients	Reduce operational challenges. Though this study is expanding to ex-US sites, only Phase 2 US patients are required to complete PRO endpoints.
Synopsis, 4.1, 6.3.6, 6.4.8, 7.1.1, 7.5.2, Appendix A, Appendix B	Revise bevacizumab exposure criteria for safety run-in patients	Reduce barriers to enrollment.
	Set Table 1 to remain on a single page	Correction.
Synopsis, 2, 6.3.4, 6.3.5, 6.3.6, 6.4.4, 6.4.5, 6.4.8, 7.4, Appendix A	Add detail regarding criteria to evaluate expansion to 70 patients	Clarification.
	Add clarity for patient replacement for DLT evaluation	Clarification.
Synopsis, 4.1	Revise eGFR inclusion criteria from eGFR ≥ 60 to eGFR ≥ 50	Reduce barriers to enrollment for patients treated with prior lines of platinum therapy.
	Clarify that cataracts are not active ocular surface disease	Clarification.
2	Move anticoagulant/anti-platelet agent decision after SMC review of run-in	Change based on updated knowledge of adverse event risk profile.
	Include antiplatelet agents as possible allowed concomitant medications after safety review	Change based on updated knowledge of adverse event risk profile.
3.1, Figure 1, 9.1	Fix table reference	Correction.
	Create consistency in instructions for lubricating eye drop use	Clarification to ensure that there are no perceived inconsistencies in instructions for lubricating eye drop use.
3.1.1	Allow scalp cooling	Patient safety/tolerability improvement.
	Fix end of Infusion PK draw window from ± 15min to +15min	Correction.
4.1	Added information regarding home health aide collection of samples	Clarification.
	Drug-induced liver injury (DILI) revision	Correction/resolution of discrepancy between DILI language and dose modifications.

Section(s)	Change	Rationale
4.2	Update AE language and reporting requirements to specify that disease progression is not an AE	Clarification.
	Add additional explanation of sample size determination and analysis to be performed when considering cohort expansion	Clarification.
4.2, 5.5.2, 5.5.3	Fix omitted detail re: PFS	Correction.
	Add definition of DLT evaluable set	Clarification.
4.2, 5.5.2, 5.5.3	Update language for Efficacy Evaluable set	Clarification/Update to analysis set definition.
	Remove 3 month PFS and 12 month OS timepoints	Reduction of unnecessary analyses.
5.2.3	Remove post-EOT PRO collection	Eliminate collection of unnecessary data.
	Fix typo to close parentheses	Typographical correction.

SUMMARY OF CHANGES IN AMENDMENT 3

Section(s)	Change	Rationale
Title page	Updated the Medical Monitor Information	Per the subject of Admin Letter 01
Title page, synopsis, footer	Updated version number and date	Administrative changes
Synopsis; throughout protocol	Edited text referring to "phase 2" portion of the study to read "Parts A and B"	Clarification. Study now contains two phase 2 cohorts
Synopsis, 4.1	Inclusion criteria changes	Cohort added; also, reduction of barriers to enrollment
Synopsis, 9.1	Number of planned patients changed	Updated number reflects added patients in Part B
Synopsis, 3.1, throughout protocol	Part B cohort added	Study design change
Synopsis, 3.1, 3.2, 5.1, 5.2.3	1.2 mg/kg dose escalation added to safety run-in	Change based on updated knowledge of adverse event risk profile in prior studies
Synopsis, 1.4	Change in DLT period	Change based on updated knowledge of adverse event risk profile.
Synopsis, 3.1	Response confirmation scan changed from "4-6 weeks" to "at least 4 weeks"	Alignment with other tisotumab vedotin protocols
Synopsis, 5.1	Infusion duration changed from 30 minutes to 30-60 minutes	Alignment with other tisotumab vedotin protocols
Synopsis, 5.1, 5.2.2, 5.6.2	Dosage cap change	Addition of 1.2 mg/kg dosing group necessitates a higher weight-based dosage cap for these patients
Synopsis,	Sample size table updates	Addition of Part B patients
Abbreviations list	"OMP" added	New abbreviation used in the text
1.3.3	Pharmacokinetics data revised	Updated PK data obtained; analysis at new 1.2 mg/kg dosing level added
1.3.3	Ocular adverse event analysis added	Change based on updated knowledge of adverse event risk profile
1.4	Pharmacokinetic and safety-related additions	Changes based on updated knowledge of adverse event risk profile and addition of new 1.2 mg/kg dosing group to the study
3.1	Study schema changed	Reflection of other design updates
3.1.1, 9.3.1.9, 9.3.9	DLT period change	Change based on updated knowledge of adverse event risk profile
3.2	Editorial changes to study design rationale	Readability
3.2.1	Descriptions added for patient assignments in safety run-in, Part A, and Part B	Necessitated by study design changes
3.2.2	Updates to dose rationale	Necessitated by study design changes (addition of 1.2 mg/kg dose escalation)
4.1, Appendix F	Contraceptive language changes	Reduction of barriers to enrollment
5.2.3	Dose delays and other modifications added	Clarification
5.3.1	Dose modifications due to ocular AEs changed	Change based on updated knowledge of adverse event risk profile

Section(s)	Change	Rationale
5.4, Appendix C	Changes to ocular prophylactic measures	Change based on updated knowledge of adverse event risk profile
6.3.1, 6.4.1, 6.4.4	Confirmation of eligibility criteria before dosing is now limited to Cycle 1 only	Reduce operational challenges
6.3.1, 6.4.1, 6.4.4, 6.4.5	Vital sign description changed to “predose vital signs”	Clarification
6.3.1, 6.4.1, 6.4.5, Appendix B	Changes to PK draw windows	Reduce operational challenges
6.3.2, 6.4.1, 6.4.2, 6.4.4, 6.4.5, 6.4.6, 6.4.7, Appendix B	Removed some blood draw samples	Eliminate collection of unnecessary data
7.4	Removal of site interventions based on patient-reported outcomes survey answers	Reduce operational challenges
9.3.1.1	Description of randomization expanded	Clarification; necessitated by study design changes
9.3.4.2	Description of TTR moved within section	Readability
Appendix A	Footnote F added to physical exam	Physical exam need not be repeated if performed within 24 hours

SUMMARY OF CHANGES IN AMENDMENT 4

Section(s)	Change	Rationale
Title page	Updated the Medical Monitor Information	Administrative change
Synopsis, Section 1.4, 3.1, 9.3.1.9, 9.3.9	Addition of interim futility analysis	Improve efficacy monitoring
Synopsis, Section 3.1, 9.1	Changed Part B to enroll approximately 80 patients	Improve efficacy monitoring
Synopsis, Section 4.1	Updated inclusion criteria	Update criteria to match benchmark patient population with high unmet need.
Section 1.1	Updated introduction regarding patient population	Update standard of care principles for platinum resistant ovarian cancer patients
Sections 4.2, 5.3.3, 5.5, 5.5.2, 5.5.3	Anticoagulation and antiplatelet therapies are permitted	Reduce barriers to enrollment.
Section 6.1	Added language clarifying that some procedures performed by the patient at home are not listed in Section 6.	Clarification
Section 6.7	Remove CA-125 blood collection from long-term follow-up	Clarification; CA-125 blood collection should coincide with imaging visits.
Appendix F	Guidance on contraception updated	Improve patient safety.