TITLE PAGE

Protocol Title:	A Randomized, Open-Label, Phase 3 Trial of Tisotumab Vedotin vs Investigator's Choice Chemotherapy in Second- or Third-Line Recurrent or Metastatic Cervical Cancer
Protocol Number:	SGNTV-003
Version; Date of Protocol:	Amendment 4; dated 22-Jan-2024
Study Name:	innovaTV 301
Investigational Drug:	Tisotumab vedotin
Study Phase:	3
Short Title:	Phase 3 Trial of Tisotumab Vedotin vs Chemotherapy in Recurrent or Metastatic Cervical Cancer
Sponsor Name and Address:	Seagen Inc.* 21823 30th Drive SE Bothell, WA 98021, USA *Please note that as of 14-Dec-2023, Seagen Inc. became part of Pfizer Inc.
Collaborator Name and Address:	Genmab A/S Kalvebod Brygge 43 DK-1560 Copenhagen V Denmark
IND No.:	135476
EudraCT No.:	2019-001655-39
EU Trial No.:	2023-503813-31

Medical Monitors:	[redacted] Seagen Inc. Tel: [redacted] Email: [redacted]	[redacted] Seagen Inc. Tel: [redacted] Email: [redacted]
ENGOT Study No.	ENGOT-cx12	ENGOT European Network of Gynaecological Oncological Trial groups
GOG Study No.	GOG-3057	GOG Foundation/Partner

DOCUMENT HISTORY AND SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Original protocol	17-Sep-2020
Amendment 1	23-Nov-2020
Amendment 2	20-Aug-2021
Amendment 3	06-Apr-2022
Amendment 4	22-Jan-2024

Amendment 1

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Protocol Amendment Summary of Changes Table: Amendment 1

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Study Schema, 1.3 Schedule of Activities, 2.1.3 Control Arm, 4.3 Justification for Dose, 6 Study Intervention, 10.7.5 Recommended Dose Modifications for Pemetrexed	Pemetrexed added as an option for investigator's choice chemotherapy arm	Increase treatment flexibility for investigators with participants in the comparator arm
6.6.1.2 Dose Delay for Tisotumab Vedotin, 7.1.1 Summary of Safety Stopping Rules	Duration of tisotumab vedotin dose delay due to toxicity changed from 12 weeks to 6 weeks before treatment is discontinued	Enhancement of participant safety
1.3, Schedule of Activities	Biomarker and PRO collection timepoints made identical for both treatment arms	Correction
5.3, Lifestyle Considerations	Added lifestyle recommendations to avoid contributing factors to the development of dry eye	Enhancement of participant safety
Throughout protocol	Sponsor company name updated	Seattle Genetics has changed its name to "Seagen Inc"
1.1 Synopsis, 4.2 Scientific Rationale for Study Design	Description of IDMC edited to be consistent with wording used in Section 9.8.1	Consistency of language throughout protocol
1.1 Synopsis, 5 Study Population	Participant number description changed to the number randomized; Definition of "Enrolled" removed	Clarification

Section # and Name	Description of Change	Brief Rationale
8.2.6 Clinical Laboratory Assessments	Pregnancy test results no longer excepted from reporting to central laboratory	Consistency of collection of results for all clinical laboratory testing
10.7 Recommended Dose Modifications for Chemotherapy Arm	Source citations added for recommended dose modifications	Compliance with best practices for study protocols

Amendment 2

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

Protocol Amendment Summary of Changes Table: Amendment 2

Section # and Name	Description of Change	Brief Rationale
Title page	Logo and study numbers for cooperative groups ENGOT and GOG added	Addition to reflect the cooperative groups on the study
Title page	[redacted] added as Seagen medical monitor. [redacted] removed as Seagen medical monitor	New medical monitor assigned to the study
1.3 Schedule of Activities	Randomization window changed from within ≤3 days of C1D1 to within ≤7 days	Time window for randomization extended to better accommodate premedication and dosing schedules for investigator's choice chemotherapy options
1.3 Schedule of Activities	Steroid eye drops are to be administered on Day -1 of each cycle	Clarification
1.3 Schedule of Activities	Row added for Patient Eye Drop Diary	Clarification
1.3 Schedule of Activities	Predose sampling for biomarker collection specified to be within 24 hours prior to dosing	Clarification
1.3 Schedule of Activities	Plasma protein and plasma DNA/RNA biomarker collection updated to include Cycles 20 and 24	Additional assessments to extend collection of biomarkers
1.3 Schedule of Activities	Separated footnotes for optional biopsy collected at time of radiographic disease progression and biopsy collected per standard of care while the participant is on study	Clarification
1.3 Schedule of Activities	Premedication for chemotherapy at C1D1 removed	Clarification

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	Existing information referenced for benefits and risks of treatment with tisotumab vedotin. Additional statements added on known and potential risks	Provision of additional information in the Benefit/Risk Assessment section in response to feedback from global regulatory authority
4.1 Overall Design 9.2 Sample Size Determination	Verbiage added to denote that no crossover is allowed in the study	Clarification
4.4.2 Study Termination	Verbiage added to define conditions for termination of the entire trial	Clarification as requested by global health authority
4.4.2 Study Termination	Verbiage added to clarify whether or not there is access to the drug once the study is completed	Clarification as requested by global health authority
5.1 Inclusion Criteria 1.1 Synopsis	Inclusion criterion for minimum age modified	Changed to allow for regional differences in age of consent
5.1 Inclusion Criteria	Calculated eGFR (MDRD formula) threshold changed from >50 mL/min/1.73m^2 to ≥50 mL/min/1.73m^2	Clarification
5.1 Inclusion Criteria	Hematological status assessment timing after transfusion changed from at least 2 weeks after transfusion to at least 1 week after transfusion	Timing of hematological status after transfusion with blood products and/or growth factor support reduced to reduce barriers to enrollment
5.1 Inclusion Criteria	Inclusion criterion 12 removed	This criterion is no longer included in late stage Seagen protocols. Biopsy tissue procurement is still required as part of screening procedures
6.6.2.2 Other AEs for Tisotumab Vedotin Section 7.1.1 Summary of Safety Stopping Rules	Permanent discontinuation of tisotumab vedotin added as a dose modification rule for bleeding events and elevated liver parameters of grade 4 severity	Changes requested by global health authority
8.2.1 Tumor Imaging	Verbiage added to clarify that tumor images may be collected for a potential blinded independent central review	Clarification
8.2.1.1 Baseline Imaging Assessments	Verbiage “if clinically suspected” added for whole-body bone scan imaging	Clarification
8.3.6 Clinical Laboratory Assessments Table 9	HbA1C removed from table of laboratory assessments	Correction
8.7.3 Tumor Tissue Sample Collection	Verbiage ‘At screening’ added to clarify timing and that biopsy collected as per standard of care was performed if participant provides consent	Clarification
9.5.6 Exploratory Analyses	Verbiage added to clarify that ADA concentration will not be summarized, only ADA incidence	Correction

Section # and Name	Description of Change	Brief Rationale
9.6.2 Safety Laboratory Tests, Vital Signs, and ECG Parameters	Verbiage added to clarify that 12-lead ECG will not be summarized	Correction
9.6.1 AEs	Verbiage added to clarify which TEAE analyses will be summarized	Correction

Amendment 3

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

Protocol Amendment Summary of Changes Table: Amendment 3

Section # and Name	Description of Change	Brief Rationale
Title Page	[redacted] added as Seagen medical monitor. [redacted] removed as Seagen medical monitor	New medical monitor assigned to the study
1.1. Synopsis 4.1. Overall Design 7.1. Discontinuation of Study Treatment 8.2.1.2. Post baseline imaging assessments	Verbiage added throughout for continued imaging to be "until evidence of radiographic disease progression or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first".	Clarification
1.3 Schedule of Activities	eGFR to be collected within 7 days of C1D1 instead of within 28 days in Tables 1 and 3	Correction
1.3 Schedule of Activities	Laboratory assessments (Hematology, Biochemistry, and Coagulation factors) and Pregnancy test moved up in Tables 1 and 3	Clarification for better visibility
1.3 Schedule of Activities	"After Cycle 1, pre-dose laboratory procedures can be conducted ≤72 hours prior to dosing" specified to be applicable to all laboratory assessments in Tables 1 and 3	Clarification
1.3 Schedule of Activities	Radiology assessments to be performed at EOT, with exception for previous tumor imaging obtained within 4 weeks	Clarification
1.3 Schedule of Activities	Health-related quality of life assessments to be collected "< 7 days" of C1D1 instead of "≤ 7 days".	Correction
1.3 Schedule of Activities	Eye drops administration specified to be 'prior to dosing'	Clarification

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	"Reference to Table 2 for detailed time points" for Anti-drug antibodies (immunogenicity) and Pharmacokinetic sampling rows in Tables 1 and 3 extended to apply to EOT visit	Clarification
1.3 Schedule of Activities	Plasma protein biomarkers removed	Change due to program-wide recommendations
1.3 Schedule of Activities	Footnote for HRQOL assessments corrected for the control arm in Table 3	Correction
1.3 Schedule of Activities	Ocular assessments and eye examination are not to be performed at unscheduled visits for the control arm, as updated in Table 3	Correction
2.1.1. Unmet Need 2.2.1. Overview of the Disease	Details of KEYNOTE-826 study and anti-PD-(L)1 therapy added	Updates to reflect changing treatment landscape
4.3. Justification for Dose 6.1.2 Chemotherapy Control Arm 10.7.1 Recommended Dose Modifications for Topotecan 10.7.2 Recommended Dose Modifications for Irinotecan	Clarified starting dose for topotecan and irinotecan	Change to provide more flexibility to physicians in treatment of trial participants
5.1 Inclusion Criteria and Synopsis	Prior anti-PD-(L)1 therapy added	Changes to reflect updated treatment landscape
5.2 Exclusion Criteria	Exclusion #6 language revised to focus on prognosis/survival	Clarification
5.2 Exclusion Criteria	Exclusion #12 amended to include exceptions for latent or controlled HIV infection.	Clarification
5.4 Screen Failures	Sponsor approval of rescreening removed.	Change to remove barriers to enrolment that did not affect patient safety
5.4 Screen Failures	Clarified that biopsy is no longer required for eligibility as per Amendment 2.	Clarification
6.1.1. Tisotumab Vedotin Arm	Physical Description updated	Changes to match updates to the Pharmacy Manual
6.3.1 Treatment Randomization	Heading removed to simplify section	Clarification
6.5.1.1. Tisotumab Vedotin Arm Premedication for Tisotumab Vedotin	"as needed" removed for self-administration of lubricating eye drops	Clarification

Section # and Name	Description of Change	Brief Rationale
6.5.3. Prohibited Concomitant Therapy	Herbal medicines removed	Change to allow enrollment of participants in regions where herbal medicines are commonly used
7.1.2.2. Survival Follow-up	Specified follow-up to start from date of EOT visit for participants who are taken off treatment before receiving any study drug	Clarification
8.4.2. Adverse Event Reporting	Safety reporting period for all AEs amended to 30 days after the last study treatment	Clarification
8.4.6. Pregnancy	Follow-up duration extended to up to 6 months of age for the child	Change to allow for longer follow-up in cases of pregnancy in accordance with regulatory agency feedback
8.7. Biomarkers	Clarified and simplified biomarker language according to current standard biomarker group language.	Clarification
(8.7.2) Biomarker Assessments in Blood Samples	Circulating tissue factor assay removed from the biomarker analysis and section removed	Assay was deemed not informative
8.7.2 Tumor Tissue Sample Collection	Verbiage added to clarify that the most recent archival tumor biopsy is to be submitted for the purposes of screening and not submitted in the case of a screen failure	Clarification

Amendment 4

This amendment is considered to be non-substantial based on the criteria set forth in Article 2 of Regulation 536/2014 of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The amendment was made to align with EU CTIS/CTR requirements.

Protocol Amendment Summary of Changes Table: Amendment 4

Section # and Name	Description of Change	Substantial Change	Brief Rationale
Title Page, page 1	Added EU Trial Number	No	To align with EU CTIS/CTR requirements
Title Page, page 1	Updated Sponsor information to include footnote: "Please note that as of 14-Dec-2023, Seagen Inc. became a part of Pfizer Inc."	No	Clarification
Title Page, page 2	[redacted] added as medical monitor. [redacted] removed as medical monitor	No	New medical monitor assigned to the study

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Open-Label, Phase 3 Trial of Tisotumab Vedotin vs Investigator's Choice Chemotherapy in Second- or Third-Line Recurrent or Metastatic Cervical Cancer

Short Title: Phase 3 Trial of Tisotumab Vedotin vs Chemotherapy in Recurrent or Metastatic Cervical Cancer

Rationale: Tisotumab vedotin is an antibody-drug conjugate (ADC) targeting tissue factor (TF). Safety and efficacy data demonstrate the potential for tisotumab vedotin to substantially improve clinical outcomes with a manageable safety profile in participants with recurrent/metastatic cervical cancer (r/mCC) who have received 1 or 2 prior lines of systemic therapy. The purpose of this trial is to evaluate the efficacy of tisotumab vedotin compared to investigator's choice of chemotherapy in participants with r/mCC who have received 1 or 2 prior lines of systemic therapy for their recurrent or metastatic disease.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Demonstrate improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with second- or third-line (2L-3L) cervical cancer	• Overall survival (OS)
Secondary	
• Assess improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with 2L-3L cervical cancer	• Progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the investigator
• Demonstrate improvement in antitumor activity of tisotumab vedotin compared to chemotherapy in participants with 2L-3L cervical cancer	• Confirmed objective response rate (ORR) based on RECIST v1.1 as assessed by the investigator
• Characterize the antitumor response of tisotumab vedotin and chemotherapy in participants with 2L-3L cervical cancer	• Time-to-response (TTR) as assessed by the investigator • Duration of response (DOR) as assessed by the investigator
• Evaluate the safety and tolerability of tisotumab vedotin	• Incidence of adverse events (AEs)
• Assess health-related quality of life (HRQOL)	• EQ-5D-5L index • EQ-5D visual analog scale (VAS) • EORTC-QLQ-C30 • EORTC-QLQ-CX24
Exploratory	
• Investigate the relationship between tumor TF expression and response to tisotumab vedotin	• Tumor TF expression (via immunohistochemistry [IHC] or RNA) in relation to efficacy endpoints
• Assess biomarkers and their association with disease, mechanisms of resistance, and/or response to therapy	• Baseline characteristics and changes from baseline of biomarkers from peripheral blood and/or formalin-

Objectives	Endpoints
	fixed paraffin-embedded (FFPE) tumor tissue in relation to efficacy endpoints
• Evaluate pharmacokinetics (PK) and immunogenicity of tisotumab vedotin	• PK concentrations and anti-drug antibodies (ADAs) associated with tisotumab vedotin

Overall Design:

This is an open-label, randomized (1:1), global, phase 3 trial of tisotumab vedotin versus investigator's choice of chemotherapy in participants with r/mCC who have received 1 or 2 prior lines of systemic therapy for their recurrent or metastatic disease. Eligible participants will be randomized to either tisotumab vedotin 2.0 mg/kg every 3 weeks (Q3W) or investigator's choice of chemotherapy (as noted in the "other study treatment" section). Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), prior bevacizumab administration (yes vs. no), region (US, EU, Other), and prior anti-programmed cell death protein 1 or anti-programmed cell death ligand 1 (anti-PD-[L]1) administration (yes vs. no). Imaging will be obtained every 6 weeks (42 days ±7 days) for the first 30 weeks and then every 12 weeks (84 days ±7 days) thereafter, calculated from Cycle 1 Day 1 (C1D1) of treatment administration. Imaging must continue until evidence of radiographic disease progression per RECIST v1.1 as assessed by investigator or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Survival status will be assessed every 60 days (±7 days) beginning from the day of the last dose of study treatment, or more frequently around the time of a database lock.

An independent data monitoring committee (IDMC), consisting of members who are external and independent of the sponsor study team, will be formed to monitor the safety of participants in this study on a periodic basis, review safety and efficacy data from this study as per planned analyses, and make recommendations to the sponsor.

Key Inclusion Criteria:

- Age ≥18 years, or considered an adult by local regulations, at time of consent.
- Has recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology, and:
- Has experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible), defined as either:
  - paclitaxel+cisplatin+bevacizumab+ anti-PD-(L)1 agent, or
  - paclitaxel+carboplatin+bevacizumab+ anti-PD-(L)1 agent, or
  - paclitaxel+topotecan/nogitecan+bevacizumab+ anti-PD-(L)1 agent

  NOTE: only in cases where bevacizumab and/or anti-PD-(L)1 agent is not a standard of care therapy or the participant was ineligible for such treatment according to local standards, prior treatment with bevacizumab and/or anti-PD-(L)1 agent is not required.

- Has received 1 or 2 prior systemic therapy regimens for recurrent and/or metastatic cervical cancer. Chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, should not be counted as a systemic therapy regimen. Single agent therapy with an anti-PD(L)1 agent for r/mCC cancer should be counted.
- Measurable disease according to RECIST v1.1 as assessed by the investigator.
- Has ECOG performance status of 0 or 1 prior to randomization.
- Has life expectancy of at least 3 months.

Key Exclusion Criteria:

- Has primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned as part of the inclusion criteria above.
- Has clinically significant bleeding issues or risks. This includes 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.
- Has any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening is allowed).
- Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis (eg, Wagner syndrome, atopic keratoconjunctivitis, autoimmune disease affecting the eyes), ocular Stevens-Johnson syndrome or toxic epidermal necrolysis, mucus pemphigoid, and participants with penetrating ocular transplants. Cataracts alone is not an exclusion criterion.
- Major surgery within 4 weeks or minor surgery within 7 days prior to the first study treatment administration.
- Peripheral neuropathy ≥grade 2.
- Any prior treatment with monomethyl auristatin E (MMAE)-containing drugs.

Number of Participants: Approximately 482 participants will be randomized in the study.

Intervention Groups and Duration:

Study Drug: Tisotumab vedotin 2.0 mg/kg Q3W

Comparator(s): Investigator's choice, <u>one</u> of the following:

- topotecan 1 or 1.25 mg/m^2 intravenous (IV) on Days 1 to 5, every 21 days
- vinorelbine 30 mg/m^2 IV on Days 1 and 8, every 21 days
- gemcitabine 1000 mg/m^2 IV on Days 1 and 8, every 21 days
- irinotecan 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days
- pemetrexed 500mg/m^2 IV on Day 1 every 21 days

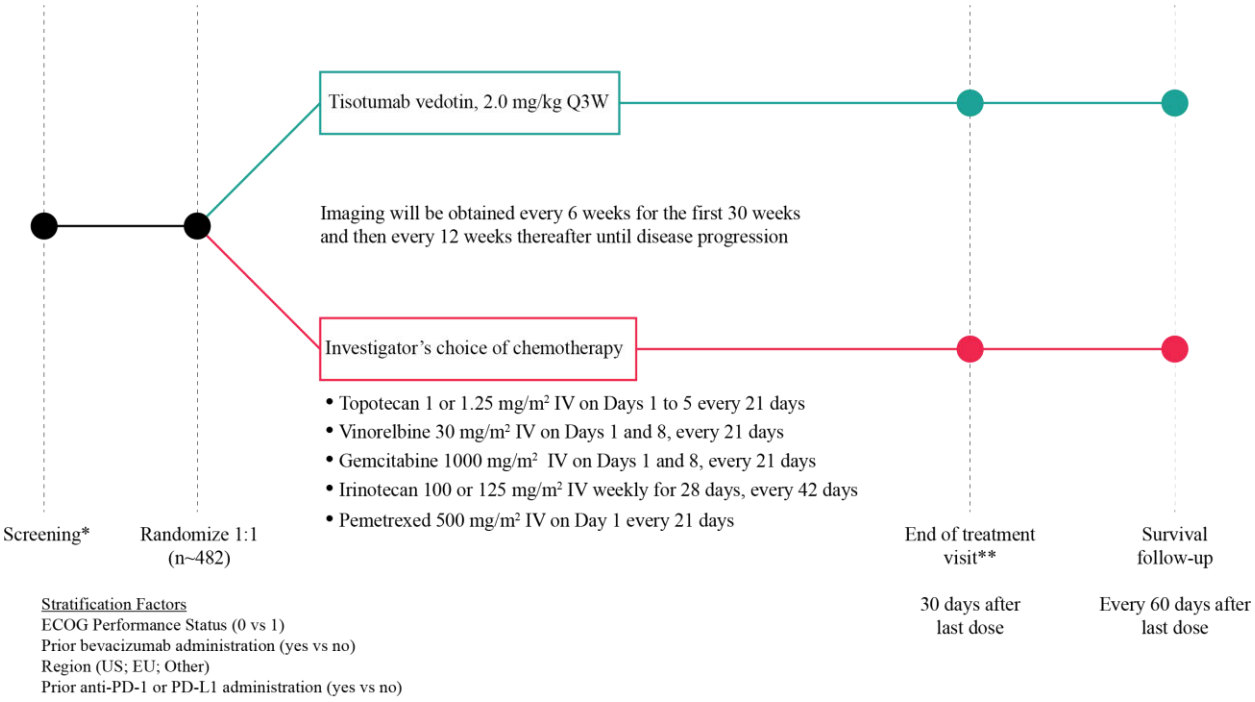
Dose Modifications: An individual's dose may be modified based upon treatment-emergent adverse events.

Data Monitoring Committee: Yes

1.2. Schema

The design of the study is shown in Figure 1.

Figure 1: Study Design



*The proportion of participants who have not received prior bevacizumab in combination with chemotherapy as 1L treatment may be capped at 50%.

** Some AESIs may be followed longer than 30 days until resolution, improvement, or stabilization.

1.3. Schedule of Activities (SoA)

Table 1 lists all the assessments in the tisotumab vedotin arm and indicates the visits to be performed and the associated timing. In addition to the fixed visits, it may be necessary to perform some of the assessments at unscheduled time points if deemed clinically necessary by the investigator. Table 2 shows the timing of the PK and ADA assessments in the tisotumab vedotin arm. Table 3 shows the timing of the assessments in the control arm (chemotherapy).

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Informed consent	Must be obtained before any study procedures are performed.		X				
Eligibility criteria		4.4.2	X				
Demographics		8	X				
Medical history		8	X				
Prior cancer history		8	X				
eGFR	Calculated eGFR (MDRD formula)	8.3.6	≤7 days of C1D1				
Hematology	After Cycle 1, pre-dose laboratory procedures can be conducted ≤72 hours prior to dosing.	8.3.6	≤7 days of C1D1	X[a]	X		X
Biochemistry		8.3.6	≤7 days of C1D1	X[a]	X		X

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			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Coagulation factors		8.3.6	≤7 days of C1D1	X[a]	X		X
Pregnancy test	For participants of reproductive potential.	10.4	≤7 days of C1D1 (serum)	X[a] (serum or urine)	X[b] (serum or urine)		X (serum or urine)
Height		8.3.1	X				
Weight	To calculate the dose of study drug for infusion.	6.1.1, 8.3.1	X	X			
Complete physical examination		8.3.1	X				
Targeted physical examination		8.3.1		X (pre-dose)	X		X

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Vital signs	Temperature, blood pressure, and heart rate at all indicated time points. Respiratory rate at screening only.	8.3.2	X	X	X		X
Electrocardiogram		8.3.3	X		X		
Randomization		6.3	≤7 days of C1D1				

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Radiology (computed tomography, magnetic resonance imaging, chest X-ray) Brain CT or MRI, whole body bone scan, and/or CT or MRI of other metastatic sites may also be required if clinically indicated	Evaluation of tumor response should be performed regardless of dosing delays.	8.2.1, Table 7	X	Q6W (±7d) for the first 30 weeks and Q12W (±7d) thereafter, calculated from the date of first tisotumab vedotin dosing until evidence of radiographic disease progression or other reasons listed in Section 7	X (not required if previous tumor imaging obtained within 4 weeks)		X
ECOG performance status		8.3.4	≤7 days of C1D1	from C2+	X		X

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Health-related quality of life EQ-5D-5L index EQ-5D VAS EORTC-QLQ-C30 EORTC-QLQ-CX24	Strongly recommended to complete prior to other assessments.	8.7.4	<7 days of C1D1	X[c]	X[d]	X[d]	
Adverse events	All AEs must be reported from first study treatment dose until the End of Treatment visit.	8.4	X	X	X		X
Peripheral neuropathy assessment	Performed for participants with ongoing peripheral neuropathy from the time of treatment discontinuation.	8.4.3			X	X	X

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Concomitant medication	To be recorded from the time of informed consent until up 30 days after the last dose of study treatment.	6.5.2, 8	X	X	X		X
Ocular assessment	Performed by optometrist or ophthalmologist at screening for baseline evaluation.	8.3.5	X				X
Eye examination	Performed by the treating physician or delegate prior to dosing. Refer to optometrist or ophthalmologist for "Ocular assessments" for any ocular events during the study within 72 hours.	8.3.5	X	X	X		X
Prophylaxis of ocular adverse events	Administered before, during, and after each TV administration.	6.5.1.1		X[e]			

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Patient Eye Drop Diary	Diary to be completed on an ongoing basis.						
Tisotumab vedotin administration	Tisotumab vedotin 2.0 mg/kg is administered as an IV infusion over a minimum of 30 minutes, recommended not to exceed 60 minutes.	6.1.1		X			
Survival status		8.2.2				X	
Hepatitis B and C	Where required by local health authorities.	8.3.6	X				
Anti-drug antibodies (immunogenicity)	Taken prior to TV administration.	8.8		Refer to Table 2 for detailed time points.			
Pharmacokinetic sampling		8.6		Refer to Table 2 for detailed time points.			

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Tumor biopsy	Must provide tumor tissue. The most recent archival tumor biopsy is preferred if collected within the last 2 years. If an archival tumor biopsy less than 2 years old is not available, a fresh tumor biopsy will be collected before initiation of study treatment, if clinically feasible. If a fresh biopsy cannot be collected, the most recent archival tumor sample may be submitted, even if obtained more than 2 years prior to participant enrollment.	Refer to Laboratory Manual	X		X[f] (optional at time of radiographic disease progression)		X[g]

Table 1: Visit Assessment Schedule for the Tisotumab Vedotin Arm

	Notes	Section Reference	Screening	Cycle 1-X (1 cycle= 21 days)	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d Prior To C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of tisotumab vedotin	As needed
Visit window				±3d	± 5d	± 7d	
Plasma DNA/RNA biomarkers	Performed within 24 hrs prior to dosing.	8.7		C1, C2, C4, C8, C12, C16, C20, C24, before tisotumab vedotin admin.	X		

a. If screening assessment is performed within 1 day of C1D1, this test does not need to be repeated on C1D1.
b. Pregnancy tests (serum or urine) are to be repeated monthly for 6 months after the last dose of tisotumab vedotin.
c. EORTC-QLQ-CX24 should be performed on D1 of every cycle for the first 20 cycles only.
d. EQ-5D-5L and EQ-5D VAS only.
e. Steroid eye drops are to be administered on Day -1 of each cycle.
f. In addition to the required baseline biopsy, an optional fresh biopsy collected at time of radiographic disease progression may be provided for biomarker analyses, if clinically feasible and if the participant provides consent for this procedure.
g. If a tumor biopsy is collected per standard of care while the participant is on study (until treatment discontinuation), the FFPE block or unstained slides may be provided for biomarker analyses, if the participant provides consent for this procedure.

Table 2: Pharmacokinetic and Anti-drug Antibodies Sampling for the Tisotumab Vedotin Arm

Cycle	Day	Time	Window	Reference Time Point	Tisotumab Vedotin Pharmacokinetics	Tisotumab Vedotin Anti-drug Antibodies
Cycle 1	1	Prior to infusion	Within 24 hrs prior to dosing	Infusion start	X	X
		End of infusion	+15 min	Infusion end	X	
	3[a]	48 hrs	± 24 hrs	Infusion start	X	
Cycle 2	1	Prior to infusion	Within 24 hrs prior to dosing	Infusion start	X	X
Cycle 4 and every fourth cycle starting from Cycle 4 (Cycle 8, Cycle 12, Cycle 16, etc.) until treatment discontinuation	1	Prior to infusion	Within 24 hrs prior to dosing	Infusion start	X	X
End of Treatment visit					X	X

a. The sample can be collected anywhere from Day 2 to Day 4 after the tisotumab vedotin administration.

Table 3: Visit Assessment Schedule for the Control Arm (Chemotherapy)

	Notes	Section Reference	Screening	Cycle 1-X[a]	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of chemotherapy	As needed
Visit window				±3d	± 5d	± 7d	
Informed consent	Must be obtained before any study procedures are performed.	10.1.10	X				
Eligibility criteria		4.4.2	X				
Demographics		8	X				
Medical history		8	X				
Prior cancer history		8	X				
eGFR	Calculated eGFR (MDRD formula)	8.3.6	≤7 days of C1D1				
Hematology[a]	After Cycle 1, pre-dose laboratory procedures can be conducted ≤72 hours prior to dosing.	8.3.6	≤7 days of C1D1	X[b]	X		X
Biochemistry[a]		8.3.6	≤7 days of C1D1	X[b]	X		X
Coagulation factors[a]		8.3.6	≤7 days of C1D1	X[b]	X		X
Pregnancy test	For participants of reproductive potential.	10.4	≤7 days of C1D1 (serum)	X[b] (serum or urine)	X[c] (serum or urine)		X (serum or urine)

Table 3: Visit Assessment Schedule for the Control Arm (Chemotherapy)

	Notes	Section Reference	Screening	Cycle 1-X[a]	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of chemotherapy	As needed
Visit window				±3d	± 5d	± 7d	
Height		8.3.1	X				
Weight	To calculate the dose of study drug for infusion.	6.1.2, 8.3.1	X	X			
Complete physical examination		8.3.1	X				
Targeted physical examination		8.3.1		X (pre-dose)	X		X
Vital signs[a]	Temperature, blood pressure, and heart rate at all indicated time points. Respiratory rate at screening only.	8.3.2	X	X	X		X
Electrocardiogram		8.3.3	X		X		
Randomization	Investigator choice of chemotherapy must be assigned and recorded for each participant prior to randomization.	6.3	≤7 days of C1D1				

Table 3: Visit Assessment Schedule for the Control Arm (Chemotherapy)

	Notes	Section Reference	Screening	Cycle 1-X[a]	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of chemotherapy	As needed
Visit window				±3d	± 5d	± 7d	
Radiology (computed tomography, magnetic resonance imaging, chest X-ray) Brain CT or MRI, whole body bone scan, and/or CT or MRI of other metastatic sites may also be required if clinically indicated	Evaluation of tumor response should be performed regardless of dosing delays.	8.2.1, Table 7	X	Q6W (±7d) for the first 30 weeks and Q12W (±7d) thereafter, calculated from the date of first chemotherapy dosing until evidence of radiographic disease progression or other reasons listed in Section 8	X (not required if previous tumor imaging obtained within 4 weeks)		X
Eastern Cooperative Oncology Group (ECOG) performance status		8.3.4	≤7 days of C1D1	from C2+	X		X

Table 3: Visit Assessment Schedule for the Control Arm (Chemotherapy)

	Notes	Section Reference	Screening	Cycle 1-X[a]	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of chemotherapy	As needed
Visit window				±3d	± 5d	± 7d	
Health-related quality of life EQ-5D-5L index EQ-5D VAS EORTC-QLQ-C30 EORTC-QLQ-CX24	Strongly recommended to complete prior to other assessments.	8.7.4	<7 days of C1D1	X[d]	X[e]	X[e]	
Adverse events[a]	All adverse events must be reported from first study treatment dose until the End of Treatment visit.	8.4	X	X	X		X
Peripheral neuropathy assessment	Performed for participants with ongoing peripheral neuropathy from the time of treatment discontinuation.	8.4.3			X	X	X
Concomitant medication	To be recorded from the time of informed consent until up to 30 days after the last dose of study treatment.	6.5.2, 8	X	X	X		X

Table 3: Visit Assessment Schedule for the Control Arm (Chemotherapy)

	Notes	Section Reference	Screening	Cycle 1-X[a]	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of chemotherapy	As needed
Visit window				±3d	± 5d	± 7d	
Ocular assessment	Performed by optometrist or ophthalmologist at screening for baseline evaluation.	8.3.5	X				
Eye examination	Performed by the treating physician or delegate. Refer to optometrist or ophthalmologist for "ocular assessments" for any ocular events during the study within 72 hours.	8.3.5	X				

Table 3: Visit Assessment Schedule for the Control Arm (Chemotherapy)

	Notes	Section Reference	Screening	Cycle 1-X[a]	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of chemotherapy	As needed
Visit window				±3d	± 5d	± 7d	
Chemotherapy administration[a]	One of the following: Topotecan 1 or 1.25 mg/m^2 IV on Days 1 to 5, every 21 days[f] Vinorelbine 30 mg/m^2 IV on Days 1 and 8, every 21 days Gemcitabine 1000 mg/m^2 IV on Days 1 and 8, every 21 days Irinotecan 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days[g] Pemetrexed 500 mg/m^2 on Day 1 every 21 days	6.2.2, 6.5.1.2		See notes			
Survival status		8.2.2				X	
Hepatitis B and C	Where required by local health authorities.	8.3.6	X				

Table 3: Visit Assessment Schedule for the Control Arm (Chemotherapy)

	Notes	Section Reference	Screening	Cycle 1-X[a]	End of Treatment Visit (Section 7.1.2)	Survival Follow-up (Section 7.1.2.2)	Unscheduled Visit
			≤ 28d prior to C1D1 unless otherwise noted	D1	30d after last dose	Q60d after last dose of chemotherapy	As needed
Visit window				±3d	± 5d	± 7d	
Tumor biopsy	Must provide tumor tissue. The most recent archival tumor biopsy is preferred if collected within the last 2 years. If an archival tumor biopsy less than 2 years old is not available, a fresh tumor biopsy will be collected before initiation of study treatment, if clinically feasible. If a fresh biopsy cannot be collected, the most recent archival tumor sample may be submitted, even if obtained more than 2 years prior to participant enrollment.	Refer to Laboratory Manual	X		X[h] (optional at time of radiographic disease progression)		X[i]
Plasma DNA/RNA biomarkers	Performed within 24 hrs prior to dosing	8.7		C1, C2, C4, C8, C12, C16, C20, C24, before chemotherapy administration	X		

a. Cycle duration and administration days vary. Refer to Section 6.1.2. In addition to the scheduled assessments, the frequency of AE collection, vital signs, and laboratory assessments should be guided by local label and guidelines for topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. If screening assessment is performed within 1 day of C1D1, this test does not need to be repeated on C1D1.
c. Pregnancy tests (serum or urine) are to be repeated monthly for 6 months after the last dose of investigator's choice chemotherapy.
d. EORTC-QLQ-CX24 should be performed on D1 of every cycle for the first 20 cycles only. In participants who receive irinotecan, EORTC-QLQ-CX24 should be performed on D1 for the first 10 cycles only.
e. EQ-5D-5L and EQ-5D VAS only.
f. For participants without significant toxicity during the first 21-day cycle of topotecan, subsequent cycles may be increased to 1.25 mg/m^2 IV × 5 days, every 21 days.
g. For participants without significant toxicity during the first 42-day cycle of irinotecan, subsequent cycles may be increased to 125 mg/m^2 IV weekly × 4, followed by 14 days off treatment.
h. In addition to the required baseline biopsy, an optional fresh biopsy collected at time of radiographic disease progression may be provided for biomarker analyses, if clinically feasible and if the participant provides consent for this procedure.
i. If a tumor biopsy is collected per standard of care while the participant is on study (until treatment discontinuation), the FFPE block or unstained slides may be provided for biomarker analyses, if the participant provides consent for this procedure.

2. INTRODUCTION

2.1. Study Rationale

High, differential levels of expression of tisotumab vedotin's target, tissue factor (TF), have been observed on the membranes of neoplastic cells as well as on tumor-associated endothelium in multiple cancers, including gynecological cancers of the cervix. Expression of TF on tumor cells has been associated with negative overall survival (OS) or disease-free survival as described in several indications. In preclinical studies, 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.

Tisotumab vedotin showed evidence of activity in 101 participants with second and third-line (3L) recurrent or metastatic cervical cancer (r/mCC) in the GCT1015-04 pivotal phase 2 trial. In the current study, tisotumab vedotin will be further examined through a randomized study design to compare against single agent chemotherapy in this patient population. Patients with r/mCC have significant unmet medical need and therefore new therapies are needed.

2.1.1. Unmet Need

Women with cervical cancer who have progressed on first-line (1L) therapy comprise a population of high unmet medical need, and the development of new therapies is crucial to address this devastating disease. This study will enroll participants with r/mCC who have experienced disease progression during or after treatment with doublet chemotherapy and bevacizumab, if deemed appropriate.

Mortality rate is high for patients with r/mCC. While patients with persistent, recurrent, or metastatic carcinoma of the cervix may receive the standard of care 1L treatment of bevacizumab and/or therapies targeting anti-programmed cell death protein 1 or anti-programmed cell death ligand 1 (anti-PD-[L]1) in combination with paclitaxel+cisplatin/carboplatin or paclitaxel+topotecan, these patients invariably progress. In addition, restrictions in the bevacizumab label and limited global availability of anti-PD-(L)1 agents suggest that a proportion of 1L patients are not eligible to receive this therapy, and thus, the standard of care for these patients is doublet chemotherapy.

In a double-blind, phase 3 trial with 1L pembrolizumab (KEYNOTE-826) in combination with standard of care treatment, progression-free survival (PFS) and OS were significantly longer with pembrolizumab than with placebo among patients with persistent, recurrent, or metastatic cervical cancer who were also receiving chemotherapy with or without bevacizumab (Colombo 2021).

No established standard of care has been identified for patients with cervical cancer who progress on or after 1L therapy. Single-agent modalities have reported response rates between 0 and 15% and an OS between 6.6 and 7.4 months (Miller 2008); (Bookman 2000); (Garcia 2007); (Muggia 2004); (Monk 2009); (Santin 2011). Furthermore, toxicity is substantial with many of these agents, thus limiting their overall benefit-risk profile.

The lack of effective treatments, high risk of relapse, and substantial toxicity associated with currently administered therapies warrant the development of novel, safe, and effective therapies that result in markedly improved clinical benefit for these patients.

2.1.2. Study Population

Tisotumab vedotin has shown activity in previously treated participants with r/mCC (see Section 2.2.3). The current study will limit inclusion to participants with 1 or 2 prior lines of systemic therapy. The eligibility criteria specify that participants must have received bevacizumab and/or anti-PD-(L)1 agent in combination with paclitaxel+carboplatin, paclitaxel+cisplatin, or paclitaxel+topotecan, if eligible to receive bevacizumab and/or anti-PD-(L)1 agent according to local standards, as these combination regimens are identified standard of care therapies for the treatment of 1L r/mCC. To ensure that the population enrolled in this study reflects the approximate global utilization of bevacizumab, the percent of participants who have not received a bevacizumab combination as a 1L therapy may be capped at 50%.

2.1.3. Control Arm

As previously mentioned, a standard of care has not been established for the r/mCC patient population, and multiple systemic therapies including chemotherapy and targeted agents have been evaluated but with very limited activity. Topoisomerase I inhibitors (ie, irinotecan, topotecan), multitargeted anti-folate (pemetrexed), antimitotic agents (ie, vinorelbine), and antimetabolite agents (ie, gemcitabine) are among the most commonly used agents and are listed as global treatment options in both the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines (Marth 2017); (Koh 2019).

The International Conference on Harmonisation (ICH) E10 guideline on “Choice of Control Group and Related Issues in Clinical Trials” indicates that in such cases where there are no standard treatment regimens and since no single regimen can be defined, an active comparator of investigator’s choice is often preferable (ICH 2000). Because this study will be conducted globally, it is necessary to minimize variables that could lead to increased heterogeneity and bias. Thus, the treatment options for the control arm from which the investigator can choose have been predefined (refer to Section 4). The specified starting doses and treatment schedules for each of the options are based on scientific literature and recommendations provided in treatment guidelines (Bookman 2000); (Muggia 2004); (Lilly USA 2018); (Takeuchi 1991); (Verschraegen 1997); (Lorusso 2010). The chemotherapy options offer different mechanisms of action and safety profiles that can be used (per investigator’s choice and local regulations) depending on the participant’s prior therapies and overall medical condition.

2.2. Background

2.2.1. Overview of the Disease

Cervical cancer has an estimated incidence of more than 500,000 new cases per year globally, accounting for approximately 8% of cancer-related deaths in female patients (Bray 2018). According to National Cancer Institute estimates, more than 291,000 women are living with invasive cervical cancer in the US, and approximately 13,800 new cases will be diagnosed in

2020. More than 4,290 women in the US will die from the disease this year (National Cancer Institute (NCI) 2020).

For the vast majority of patients diagnosed with r/mCC, platinum-based chemotherapy regimens were the 1L standard of care for many years. More recently, a systemic combination therapy of bevacizumab with either cisplatin+paclitaxel or paclitaxel+topotecan was established as the standard of care for 1L treatment of patients with persistent, r/mCC based on the Gynecologic Oncology Group (GOG) 240 trial. Median OS was increased by 3.7 months in the bevacizumab arm (17.0 months vs. 13.3 months with chemotherapy alone, hazard ratio [HR] 0.71). The objective response rate (ORR) was substantially higher in the bevacizumab arm (48% vs. 36%), and PFS was substantially prolonged (8.2 months vs. 5.9 months) (Tewari 2014). The addition of bevacizumab to chemotherapy was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%). This regimen is the standard of care for the 1L treatment of r/mCC for patients who are eligible to receive bevacizumab. While definitive data are lacking, physician surveys suggest that approximately 55% and 47% of patients with cervical cancer in the US and Europe, respectively, are treated with the GOG 240 regimen in the 1L setting (cancermpact.com).

In the KEYNOTE-826 study, pembrolizumab, an anti-PD-(L)1 agent, met the dual primary endpoints of PFS and OS in patients with persistent, recurrent, or metastatic cervical cancer who were also receiving chemotherapy with or without bevacizumab (Colombo 2021).

Treatment options after the 1L are limited, and no standard of care therapies have been identified. Single-agent cytostatic therapies are the mainstay of treatment; however, median survival is <9 months, and robust phase 2 or 3 data are lacking. Multiple cytostatic agents for the treatment of patients with cervical cancer who progress on or after 1L treatment are available, including vinorelbine, topotecan, irinotecan, pemetrexed, gemcitabine, or nanoparticle albumin-bound paclitaxel. However, modest response rates and limited evidence of durability are observed with these therapies (Marth 2017); (Koh 2019).

Recently, pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, received accelerated approval in the US for the treatment of patients with programmed cell death ligand 1 (PD-L1) positive (combined proportioned score ≥1) or microsatellite instability high/deficient mismatch repair cervical cancer who have demonstrated disease progression on or after chemotherapy. An ORR of 14% and a disease control rate of 31% was observed among 77 previously treated patients with advanced cervical cancer who had PD-L1 expression of ≥1% (Merck & Co Inc 2018).

2.2.2. Introduction to the Investigational Medicinal Product

TF is a transmembrane glycoprotein that in normal physiology is the main initiator of the extrinsic coagulation pathway. In malignant cells, strict regulation of TF is lost, and it is aberrantly expressed in tumor cells and associated stromal cells of the tumor microenvironment. Published reports and sponsor studies demonstrate TF expression in a variety of malignancies, often correlating with increased metastatic properties, angiogenesis, tumor initiation, tumor growth, and poor disease prognosis (Kakkar 1995; Rickles 1995; Sawada 1999; Kaushal 2008; Milsom 2008; Cocco 2011a). Procoagulant activity and intracellular signaling induced by TF may enhance metastatic potential, angiogenesis, and cell survival in tumor cells (Ruf 1996).

Immunohistochemistry (IHC) analysis of TF expression in cervical cancer tissue (adenocarcinoma and squamous cell carcinoma) demonstrated high prevalence of TF expression in the tested patient population, with 96% of evaluable patient biopsies showing TF expression at variable intensities (Data on file from GCT1015-04 pivotal phase 2 trial). Comparison between cervical cancer biopsies and a small set of normal cervix biopsies showed enhanced TF staining intensity and a higher frequency of TF-positive cells in malignant tissues, demonstrating differential expression (Cocco 2011b; Srinivasan 2011).

The investigational medicinal product, tisotumab vedotin, is an antibody-drug conjugate (ADC) composed of a human monoclonal immunoglobulin G1 (subtype κ) targeting TF 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 (Chen 2017).

Tisotumab vedotin binds to TF-expressing tumor cells, followed by internalization of the ADC-TF complex, and the local release of MMAE via proteolytic cleavage (Breij 2014). MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. Released MMAE can diffuse out of the cell into the tumor microenvironment and enter neighboring cells by passive diffusion (Okeley 2010). If the neighboring cell is undergoing active cell division, then MMAE can once again induce cell cycle arrest and apoptotic death–a process called bystander cytotoxicity–independent of the neighboring cell's TF expression level (Breij 2014). The direct cytotoxicity of Tisotumab vedotin may be augmented by the immune-mediated tumor cell killing effects of antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and immunogenic cell death clinic (Alley 2019). Finally, in vivo anti-tumor activity of tisotumab vedotin was demonstrated in multiple tumor types in mouse efficacy models implanted with cell line-derived and patient-derived tumor xenografts.

Tisotumab vedotin had no toxicologically meaningful effects on coagulation and bleeding events in cynomolgus monkeys with regards to untoward secondary effects of binding TF. While in vitro evidence suggests biological plausibility for tisotumab vedotin to alter TF-dependent initiation of coagulation, downstream physiological processes related to coagulation and bleeding have not manifested nonclinically. Further details of nonclinical studies can be found in the Investigator's Brochure.

2.2.3. Summary of Clinical Trials

Tisotumab vedotin is in clinical development for the treatment of various solid tumors expressing TF, including cervical cancer. As of July 2020, there are 8 completed or ongoing clinical trials with tisotumab vedotin for the treatment of cervical cancer and other solid tumors: GEN701, GEN702, GCT1015-03, GCT1015-04, GCT1015-05, GCT1015-06, SGNTV-001, and SGNTV-002.

GCT1015-04 is a pivotal phase 2, single-arm, global trial of tisotumab vedotin in 101 participants with previously treated recurrent or metastatic cervical cancer. Eligible participants had 2L or 3L r/mCC and had experienced disease progression on or after receiving a chemotherapy doublet (paclitaxel + cisplatin/carboplatin OR paclitaxel + topotecan) in combination with bevacizumab, if eligible to receive such treatment/s according to local standards. Prior chemoradiation with curative intent was not considered a line of therapy for the

purposes of the trial. Participants were treated with IV tisotumab vedotin 2.0 mg/kg every 3 weeks (Q3W) until disease progression or unacceptable toxicity. Imaging was obtained every 6 weeks for the first 30 weeks and every 12 weeks thereafter until each participant experienced disease progression, began a new anti-cancer therapy, withdrew from the trial, or died. Responses were confirmed at least 4 weeks (28 days) after the first assessment of response.

The primary endpoint was confirmed ORR based upon Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, assessed by independent review committee (IRC). Secondary endpoints included duration of response (DOR), time to response (TTR) and PFS assessed by IRC and confirmed ORR, DOR, TTR, and PFS assessed by investigator, OS, and safety and tolerability. All radiographic secondary efficacy endpoints were based upon RECIST v1.1.

At the 06 Feb 2020 data cutoff for primary analysis, treatment with tisotumab vedotin in GCT1015-04 resulted in a clinically meaningful confirmed ORR per IRC of 24% [95% CI: 15.9%-33.3%] in participants with previously treated r/mCC, with 7 participants achieving a complete response (CR). Responses were generally consistent with the overall trial population across the subgroups analyzed and observed regardless of TF expression levels.

Responses were durable, with a median DOR of 8.3 months (95% CI 4.2 months – not reported [NR]). This DOR compares favorably with the limited DOR data available for single agent chemotherapies, which present historical median DORs ranging from 3 to 6 months. Additionally, an estimated 62% of responses to tisotumab vedotin remained ongoing at 6 months.

Tisotumab vedotin had a manageable and tolerable safety profile in this population of 2L and 3L participants with recurrent or metastatic cervical cancer. The most common treatment-emergent adverse events (TEAEs) included nausea (41 participants, 41%), alopecia (39 participants, 39%), epistaxis (39 participants, 39%), fatigue (35 participants, 35%), anemia (34 participants, 34%), and conjunctivitis (31 participants, 31%).

Certain TEAEs are identified as adverse events of special interest (AESIs) as follows: bleeding adverse event (AE) (TF plays a key physiologic role in clotting initiation); ocular AE (hypothesized as TF-mediated, due to TF expression on conjunctiva); peripheral neuropathy (known neurotoxic potential of MMAE). These AESIs including ocular AEs, peripheral neuropathy, and bleeding events were generally mild to moderate in nature (grades 1 and 2) and were effectively managed with dose modifications and supportive care. Please refer to the Investigator's Brochure for additional information.

In summary, the efficacy and safety data from GCT1015-04 demonstrate the potential for tisotumab vedotin to substantially improve clinical outcomes with a manageable safety profile in participants with r/mCC with disease progression on or after chemotherapy.

2.3. Benefit/Risk Assessment

Data from GCT1015-04 demonstrate clinically meaningful efficacy of tisotumab vedotin in participants with r/mCC along with a manageable safety profile (Section 2.2.3). Given the limited efficacy achieved with currently available therapies for patients with advanced or metastatic cervical cancer (Section 2.1.1), safety and efficacy data from the GCT1015-04 trial suggest a positive benefit-risk profile and warrant further investigation of tisotumab vedotin in participants with cervical cancer who have progressed on 1L therapy. This population represents

a substantial high unmet need and further investigation of treatments such as tisotumab vedotin that have novel mechanisms of action are needed to potentially extend and improve the quality of the lives of these patients. Known risks to participants from tisotumab vedotin include ocular adverse events, peripheral neuropathy, and epistaxis. Potential risks include bleeding events, cytopenia, skin toxicity, gastrointestinal disorders, and infusion-related reactions. Additional potential risks as described in the Investigator's Brochure pertain to pregnancy and lactation and immunogenicity.

The following risk mitigation measures are being employed to ensure the safety of participants in this trial:

- Formation of an independent data monitoring committee (IDMC) to monitor safety of tisotumab vedotin in participants.
- Identification of AESIs and implementation of preventative mitigation measures for each, when appropriate (see Section 6.6.2), that are informed by prior clinical trials as well as thought leader input.

Preliminary safety and activity data from the tisotumab vedotin clinical trials suggest a positive benefit-risk profile. More detailed information about the known and expected benefits and risks and reasonably expected AEs of tisotumab vedotin may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 4.

Table 4: Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• Demonstrate improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with 2L-3L cervical cancer	• OS
Secondary	
• Assess improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with 2L-3L cervical cancer	• PFS based on RECIST v1.1 as assessed by the investigator
• Demonstrate improvement in antitumor activity of tisotumab vedotin compared to chemotherapy in participants with 2L-3L cervical cancer	• Confirmed ORR based on RECIST v1.1 as assessed by the investigator
• Characterize the antitumor response of tisotumab vedotin and chemotherapy in participants with 2L-3L cervical cancer	• Time-to-response (TTR) as assessed by the investigator • DOR as assessed by the investigator
• Evaluate the safety and tolerability of tisotumab vedotin	• Incidence of AEs
• Assess health-related quality of life (HRQOL)	• EQ-5D-5L index • EQ-5D visual analog scale (VAS) • EORTC-QLQ-C30 • EORTC-QLQ-CX24
Exploratory	
• Investigate the relationship between TF tumor expression and response to tisotumab vedotin	• Tumor TF expression (via immunohistochemistry [IHC] or RNA) in relation to efficacy endpoints
• Assess biomarkers and their association with disease, mechanisms of resistance, and/or response to therapy	• Baseline characteristics and changes from Baseline of biomarkers from peripheral blood and/or formalin-fixed paraffin-embedded (FFPE) tumor tissue in relation to efficacy endpoints
• Evaluate the pharmacokinetics (PK) and immunogenicity of tisotumab vedotin	• PK concentrations and anti-drug antibodies (ADAs) associated with tisotumab vedotin

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, randomized (1:1), global, phase 3 study of tisotumab vedotin versus investigator's choice of chemotherapy in participants with r/mCC who have received 1 or 2 prior lines of systemic therapy for their recurrent or metastatic disease. Eligible participants will be randomized to either tisotumab vedotin 2.0 mg/kg Q3W or investigator's choice of chemotherapy (See Section 4.3). No crossover between treatment arms is permitted. The term "study treatment" is used hereafter to refer to either tisotumab vedotin or any of the chemotherapy options.

Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), prior bevacizumab administration (yes vs. no), region (US, EU, Other), and prior anti-PD-(L)1 administration (yes vs. no). Imaging will be obtained every 6 weeks (42 days ±7 days) for the first 30 weeks and then every 12 weeks (84 days ±7 days) thereafter, calculated from Cycle 1 Day 1 (C1D1) of treatment administration. Imaging must continue until evidence of radiographic disease progression per RECIST v1.1 as assessed by investigator (see Section 7.1.2) or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Survival status will be assessed every 60 days (±7 days) beginning from the day of the last dose of study treatment, or more frequently around the time of a database lock. Approximately 482 participants will be randomized in the study. The design schema of the study is shown in Section 1.2.

4.2. Scientific Rationale for Study Design

Participants will be randomized 1:1 to one of the 2 arms to minimize bias in the assessment of treatment effects. The investigator's choice of chemotherapy must be assigned and recorded for each participant prior to randomization. Randomization will be stratified by ECOG performance status, prior bevacizumab, region, and prior anti-PD-(L)1 therapy, as these are considered medically important prognostic factors and to ensure balance across these treatment groups, which could potentially influence the primary outcome, OS. The proportion of participants who have not received prior bevacizumab in combination with chemotherapy as 1L treatment may be capped at 50%, given that 50% represents the approximate utilization of bevacizumab in combination with chemotherapy as 1L standard of care in patients with cervical cancer.

Blinding of the study is not operationally feasible due to the substantial differences in toxicity profile, cycle lengths, treatment administration, and premedications of the control arm treatment. Therefore, the study design will be open-label with the investigator, participants, and sponsor unblinded to treatment assignment. The evaluation of clinical effectiveness will be based on OS, which was selected as the primary endpoint as the most relevant and preferred endpoint in oncology in accordance with regulatory guidance.

As no approved standard of care is available in the study population, the comparator treatment for tisotumab vedotin is investigator's choice from a set of defined, available, commonly used chemotherapies in this setting. An interim analysis (IA) will be conducted to enable a potentially earlier assessment of whether tisotumab vedotin clearly prolongs OS compared to chemotherapy. An IDMC, consisting of members who are external and independent of the sponsor study team, will be formed to monitor the safety of participants in this study on a periodic basis, review

safety and efficacy data from this study as per planned analyses, and make recommendations to the sponsor. Refer to the IDMC charter for details.

4.3. Justification for Dose

Participants will be treated with either tisotumab vedotin 2.0 mg/kg IV Q3W or investigator's choice of chemotherapy. The 2.0 mg/kg dose of tisotumab vedotin was identified as the recommended phase 2 dose in Part 1 of Trial GEN701 and was further evaluated in multiple dose-expansion cohorts during which additional safety and efficacy data were collected. The investigator's choice chemotherapy options are:

- Topotecan 1 or 1.25 mg/m^2 IV on Days 1 to 5, every 21 days
- Vinorelbine 30 mg/m^2 IV on Days 1 and 8, every 21 days
- Gemcitabine 1000 mg/m^2 IV on Days 1 and 8, every 21 days
- Irinotecan 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days
- Pemetrexed 500 mg/m^2 on Day 1, every 21 days

Although there is no defined standard of care treatment for patients with r/mCC who have progressed during or after 1L treatment, there are small, single-agent, single-institution trials that support the use of certain chemotherapies in this setting (Table 5). These chemotherapy options and the respective doses and schedules are considered acceptable treatment options for a control arm and are all, or mostly, included in the NCCN (Koh 2019), ESMO (Marth 2017), and Japanese guidelines (Ebina 2019).

Table 5: Clinical Outcomes in the Second Line and Beyond

Author	Agent	N	ORR (%)	PFS	OS
(Muggia 2004)	Vinorelbine	44	13.7	NR	NR
(Bookman 2000)	Topotecan	45	12.5	2.1 months	6.6 months
(Schilder 2005)	Gemcitabine	22	4.5	2.1 months	6.5 months
(Verschraegen 1997)	Irinotecan	42	21	NR	6.4 months
(Lorusso 2010)	Pemetrexed	43	13.9	10 weeks	35 weeks

4.4. End of Study Definition

4.4.1. End of Study Definition

The study is considered completed when the last survival follow-up visit is completed or 5 years after randomization of the last participant participating in the study, whichever occurs first.

4.4.2. Study Termination

The sponsor reserves the right to close a site or terminate the study at any time for any reason at the sole discretion of the sponsor. Safety will be monitored throughout the study. If new or emerging safety information that affects the benefit/risk assessment of the trial negatively emerges, the trial will be discontinued. Sites will be closed upon study completion.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for early closure of a site by the sponsor or investigator include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) or local health authorities, the sponsor's procedures, or ICH Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further tisotumab vedotin development
- If the development of the tisotumab vedotin is discontinued, or study closure is necessary, the sponsor will ensure provisioning of post-study treatment for ongoing study participants

The sponsor will consult with the investigator, as appropriate, regarding the potential for continuation of study treatment for any participant continuing to benefit from tisotumab vedotin at the time the study is completed.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Each potential participant must fulfill all of the following criteria to be enrolled in the study. Note that further inclusion criteria may apply to each of the chemotherapy options and that the investigator should assess eligibility based upon local labeling or institutional guidelines prior to identifying the chemotherapy they would administer, if the participant is randomized to the control arm.

1. Age ≥18 years, or considered an adult by local regulations, at time of consent.
2. Must sign an informed consent form (ICF) indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study prior to any other study-related assessments or procedures.
3. Has recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology, and:
   a. Has experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible), defined as either:
      – paclitaxel+cisplatin+bevacizumab+ anti-PD-(L)1 agent, or
      – paclitaxel+carboplatin+bevacizumab+ anti-PD-(L)1 agent, or
      – paclitaxel+topotecan/nogitecan+bevacizumab+ anti-PD-(L)1 agent

   NOTE: only in cases where bevacizumab and/or anti-PD-(L)1 agent is not a standard of care therapy or the participant was ineligible for such treatment according to local standards, prior treatment with bevacizumab and/or anti-PD-(L)1 agent is not required.

   b. Has received 1 or 2 prior systemic therapy regimens for recurrent and/or metastatic cervical cancer. Chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, should not be counted as a systemic therapy regimen. Single agent therapy with an anti-PD(L)1 agent for r/mCC should be counted.
   c. Is not a candidate for curative therapy, including but not limited to radiotherapy or exenterative surgery.
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 participant 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. Must demonstrate acceptable screening laboratory values:

	Laboratory Test	Value
	Renal Function	
A1	Calculated eGFR (MDRD formula)	≥50 mL/min/1.73m^2
	Liver Function	
B1	Alanine aminotransferase (ALT)	≤3× upper limit of normal (ULN) (if liver tumor/metastases are present, then ≤5×ULN is allowed)
B2	Aspartate aminotransferase (AST)	≤3×ULN (if liver tumor/metastases are present, then ≤5×ULN is allowed)
B3	Bilirubin	≤1.5×ULN (except in participants diagnosed with Gilbert's syndrome, direct bilirubin ≤2×ULN)
	Hematological Status[a] (assessed at least 1 week after transfusion with blood products and/or growth factor support)	
C1	Hemoglobin	≥5.6 mmol/L (9.0 g/dL)
C2	Absolute neutrophil count (ANC)	≥1500/µL (1.5x10^9/L)
C3	Platelet count	≥100×10^9/L
	Coagulation Status[b] **For participants NOT on anti-coagulation therapy**	
D1	Activated partial thromboplastin time (aPTT)	≤1.5×ULN
D2	International normalized ratio (INR)	≤1.2
	Coagulation Status[b] **For participants on anti-coagulation therapy**[c]	
E1	aPTT	≤1.5×ULN
E2	INR	≤2.5[d]

a. Acceptable hematologic status must be met without erythropoietin administration and packed red blood cell transfusion or G-CSF within 1 week of C1D1.
b. Acceptable coagulation status must be met within 1 week of C1D1
c. Concurrent chronic use of prophylactic acetylsalicylic acid (eg, aspirin) or chronic anti-platelet therapy is prohibited for participants on any type of anti-coagulation therapy.
d. Participants that require laboratory assessments for dose titration (warfarin or other vitamin K dependent anticoagulant agents) must be on a steady dose (no active titration) for ≥4 weeks prior to C1D1.

6. Has ECOG performance status of 0 or 1 prior to randomization.
7. Has life expectancy of at least 3 months.
8. Has a negative serum pregnancy test for participants of reproductive potential. Participants that are postmenopausal, permanently sterilized or previously subjected to bilateral oophorectomy, bilateral salpingectomy and/or hysterectomy can be considered as not having reproductive potential (refer to Section 10.4).
9. Participants of reproductive potential must agree to use adequate contraception during and for 6 months after the last study treatment administration. Adequate contraception is

defined as highly effective methods of contraception (refer to Section 10.4). Two highly effective methods of contraception must be used in countries where this is required.

10. Must agree not to breastfeed or donate ova, starting at the time of informed consent and continuing through 6 months after receiving the last dose of study drug administration.
11. Where required by local health authorities, has negative serology for hepatitis B surface antigen (HBsAg)/HBV DNA, or hepatitis C antibody (HCVAb) or RNA. Active hepatitis C is defined by a known positive HCVAb result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
12. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5.2. Exclusion Criteria

A potential participant who meets any of the following criteria will be excluded from participating in the study. Note that further exclusion criteria may apply to each of the chemotherapy options and that the investigator should assess eligibility based upon local labeling or institutional guidelines prior to identifying the chemotherapy they would administer, if the participant is randomized to the control arm.

1. Has primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned in inclusion criterion 3 (refer to Section 5.1).
2. Has clinically significant bleeding issues or risks:
    a. Known past or current coagulation defects leading to an increased risk of bleeding
    b. Diffuse alveolar hemorrhage from vasculitis
    c. Known bleeding diathesis
    d. Ongoing major bleeding (ie, participant requires a transfusion of >2 platelet concentrates within 14 days of the first dose of study treatment)
    e. Trauma with increased risk of life-threatening bleeding
    f. History of severe head trauma or intracranial surgery within 8 weeks of study entry.
3. Has cardiovascular issues or risks:
    a. Clinically significant cardiac disease, including unstable angina or acute myocardial infarction, 6 months prior to screening
    b. Any medical history of congestive heart failure (grade III or IV as classified by the New York Heart Association)
    c. Any medical history of decreased cardiac ejection fraction of <45%
    d. A marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval >450 msec)
    e. A complete left bundle branch block (defined as a QRS interval ≥120 msec in left bundle branch block form) or an incomplete left bundle branch block
4. Central nervous system (CNS): any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening is allowed).

5. Ophthalmological: Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis (eg, Wagner syndrome, atopic keratoconjunctivitis, autoimmune disease affecting the eyes), ocular Stevens-Johnson syndrome or toxic epidermal necrolysis, mucus pemphigoid, and participants with penetrating ocular transplants are ineligible. Cataracts alone is not an exclusion criterion.
6. Other cancer: known past or current malignancy other than inclusion diagnosis. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS ≥90%) such as non-invasive basal cell or squamous cell skin carcinoma, non-invasive, superficial bladder cancer, and ductal carcinoma in situ.
7. Brain metastases are allowed if the following criteria are met: definitive therapy (eg, surgery or stereotactic brain radiotherapy) has been completed >8 weeks before the first dose of study treatment; no evidence of clinical or radiologic progression of the brain metastases; participant has completed perioperative corticosteroid therapy or steroid taper. NOTE: Chronic steroid therapy is acceptable provided that the dose is stable for 1 month prior to screening.
8. Surgery/procedures: major surgery within 4 weeks or minor surgery within 7 days prior to the first study treatment administration. Participants must have recovered adequately from the toxicity or complications from the intervention prior to starting study treatment. Participants who have planned major surgery during the treatment period must be excluded from the study.
9. Peripheral neuropathy ≥grade 2.
10. Prior anti-cancer therapy:
    a. Any prior treatment with MMAE-derived drugs.
    b. Radiotherapy within 21 days prior to the first administration of study treatment. Participants must have recovered from all clinically significant radiation-related toxicities. At least 42 days must have elapsed from the last administration of chemo-radiotherapy.
    c. Small molecules, chemotherapy, immunotherapy, or monoclonal antibodies within 28 days prior to the first administration of study treatment.
    d. Currently participating in or has participated in a study of an investigational agent or device and received active treatment within 28 days prior to the first dose of study treatment.
11. Other:
    a. Ongoing significant, uncontrolled medical condition.
    b. Clinically significant active viral, bacterial, or fungal infection requiring IV or oral treatment with antimicrobial therapy ending <7 days prior to first study treatment administration.
    c. Clinically relevant bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage.
    d. Participants with clinical symptoms or signs of gastrointestinal obstruction and who require parenteral hydration or nutrition at the time of the first dose of study treatment.

12. Has known seropositivity of human immunodeficiency virus (HIV); known medical history of hepatitis B or C infection. Note: No testing for HIV, hepatitis B, or hepatitis C is required, unless mandated by local health authorities. Exceptions include latent or controlled HIV infection.
13. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (dose exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of tisotumab vedotin.
14. Is pregnant or intends to conceive children within 6 months of ending study treatment.
15. Is breast feeding and cannot discontinue breast feeding for the duration of the study and ≥6 months after the last study treatment administration.
16. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments.
17. Known allergies, hypersensitivity, or intolerance to study treatment or its excipients (refer to the Investigator's Brochure for further information on tisotumab vedotin).
18. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

5.3. Lifestyle Considerations

Participants who receive tisotumab vedotin are advised not to wear contact lenses during the treatment phase of the study.

To minimize possible contributing factors to the development of dry eye during the treatment phase of the study, participants are encouraged to cleanse the face and thoroughly remove makeup nightly, especially around the eyelids and eyelashes (ie, to remove eye shadows, mascara, and eye liner).

Also to minimize dry eye, it is recommended that participants limit screen time on digital/electronic devices during the treatment phase of the study. The sponsor recommends the "20/20/20 Rule": for every 20 minutes spent focusing on a digital screen, spend at least 20 seconds looking at an object that is at least 20 feet away. In addition, it is recommended to adjust indoor lighting to avoid glare on electronic devices.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreened participants should be assigned a different participant number from the initial screening. Upon rescreening, all eligibility criteria must be re-assessed by the investigator.

Results from assessments performed during the previous screening period are acceptable for rescreening purposes if performed within the specified time frame and the inclusion/exclusion criteria are met:

- Previously obtained chest X-ray (CXR), computed tomography (CT) or magnetic resonance imaging (MRI) scans are valid for rescreening purposes if the scanning acquisition date is ≤28 days prior to C1D1.
- Already completed HRQOL questionnaires are valid if they have been completed ≤7 days prior to C1D1.
- Blood samples taken during the previous screening process are valid for rescreening purposes as long as they fulfill the initial timelines as indicated in Table 1 and Table 3. The same tumor biopsy sample is valid for rescreening purposes.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

The term “study treatment” is used hereafter to refer to either:

- tisotumab vedotin 2.0 mg/kg every 21 days (Q3W), or
- any of the chemotherapy options. The investigator's choice chemotherapy options are:
  - Topotecan 1 or 1.25 mg/m^2 IV on Days 1 to 5, every 21 days
  - Vinorelbine 30 mg/m^2 IV on Days 1 and 8, every 21 days
  - Gemcitabine 1000 mg/m^2 IV on Days 1 and 8, every 21 days
  - Irinotecan 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days
  - Pemetrexed 500 mg/m^2 on Day 1, every 21 days

Study treatment will be administered until one of the criteria for treatment discontinuation is met (see Section 7.1).

6.1.1. Tisotumab Vedotin Arm

Tisotumab Vedotin

Tisotumab vedotin is an ADC composed of an IgG1 human monoclonal antibody chemically conjugated via a protease cleavable valine citrulline linker to the drug MMAE.

Physical Description of Tisotumab Vedotin

Tisotumab vedotin is presented as a lyophilized powder for reconstitution in water for injection and is intended for IV dosing by infusion after dilution in physiological saline solution, 5% Dextrose Injection, USP; or Lactated Ringer’s Injection, USP. It is manufactured and provided under the responsibility of the sponsor. A list of excipients can be found in the Investigator’s Brochure.

Tisotumab Vedotin Dosage and Administration

Tisotumab vedotin 2.0 mg/kg will be administered as an IV infusion on Day 1 of each 3-week treatment cycle (21 days) after all procedures and assessments have been completed. Tisotumab vedotin should be administered over a minimum of 30 minutes and it is recommended not to exceed 60 minutes. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

Each participant’s dose will be calculated based on the participant’s weight (as described in Section 8.3.1) and may be rounded to the nearest kilogram, ie, 2.0 mg/kg × body weight in kg. For participants who weigh >100 kg, the calculation of the tisotumab vedotin dose should be normalized to 100 kg (ie, 2.0 mg/kg × 100 kg = 200 mg).

The Pharmacy Manual contains specific instructions for the preparation of the tisotumab vedotin infusion and administration of infusion solution.

As a routine precaution, participants dosed with tisotumab vedotin must be monitored during infusion and treated in an area with resuscitation equipment and emergency agents. All participants should be observed for 2 hours after ending their first infusion of tisotumab vedotin and 15 minutes for all subsequent cycles.

Preventive eye therapy must be administered in relation to each administration of tisotumab vedotin as described in Section 6.5.1.1.

6.1.2. Chemotherapy Control Arm

The investigator's choice chemotherapy options are:

- Topotecan 1 or 1.25 mg/m2 IV on Days 1 to 5, every 21 days
- Vinorelbine 30 mg/m2 IV on Days 1 and 8, every 21 days
- Gemcitabine 1000 mg/m2 IV on Days 1 and 8, every 21 days
- Irinotecan 100 or 125 mg/m2 IV weekly for 28 days, every 42 days
- Pemetrexed 500 mg/m2 on Day 1, every 21 days

For the investigator's choice of chemotherapy options, doses are weight-based. For C1D1, the investigator should use screening weight to calculate the dose, but C1D1 weight is also allowed to be used, per investigator discretion. Weight is measured at the start of each cycle. If there is a ≥10% change in weight, the investigator's choice chemotherapy dose should be recalculated.

6.2. Preparation/Handling/Storage/Accountability

General Procedures

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Binder.

6.2.1. Tisotumab Vedotin

Packaging and Labeling of Tisotumab Vedotin

Tisotumab vedotin will be supplied to the study site pharmacy as single vial cartons. 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 applicable local regulatory requirements. For further details, please refer to the Pharmacy Binder.

Preparation, Handling, and Storage of Tisotumab Vedotin

Tisotumab vedotin (lyophilized vials) must be stored in a refrigerator at 2°C to 8°C. The dose of tisotumab vedotin for administration must be prepared by the study site pharmacy using aseptic technique. The reconstituted tisotumab vedotin must be diluted into 0.9% NaCl 100 mL infusion bag according to the dose calculated for the participant. Refer to the Pharmacy Manual for instructions on storage, preparation, and infusion of tisotumab vedotin.

6.2.2. Chemotherapy Control Arm

Topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed will be provided or reimbursed by the sponsor. Refer to the Pharmacy Binder and local label for instructions on storage, preparation, and administration.

6.2.3. Drug Accountability

The investigator or designee should maintain an accurate record of the shipment and dispensing of study treatment in accordance with the transactions in the Randomization and Trial Supply Management (RTFM) system. Drug accountability will be verified by the field monitor during site visits and at the completion of the study.

Drug accountability procedures are provided in the Pharmacy Binder.

6.2.3.1. Technical Complaint Handling

A technical complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A technical complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of technical complaint information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of technical complaint information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial technical complaints must be reported to the sponsor by the site personnel within 24 hours after being made aware of the event.

If the defect is combined with an AE, the site personnel must report the AE to the sponsor according to the AE and SAE reporting process and timelines (Section 8.4) in addition to

reporting the technical complaint. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Although this is an open label study, to maintain trial integrity, analyses or summaries by randomized treatment or actual treatment assignment will be limited and documented while the study is ongoing and before the database lock for primary analyses.

Randomization will be used to avoid bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. The study has 2 treatment arms, and randomization will occur centrally using an RTSM system. Participants will be assigned randomly in a 1:1 ratio to either tisotumab vedotin or chemotherapy. The investigator's choice of chemotherapy must be assigned and recorded for each participant prior to randomization. Additionally, the proportion of participants who have not received prior bevacizumab in combination with chemotherapy as 1L treatment may be capped at 50%. Randomization will be stratified according to the following factors:

- ECOG performance status: 0 vs. 1
- Prior bevacizumab therapy: yes vs. no
- Prior anti-PD-(L)1 therapy: yes vs. no
- Region: US, EU, Other

6.4. Study Intervention Compliance

Study drug will be administered by site personnel to assure compliance with study requirements.

6.5. Concomitant Therapy

6.5.1. Premedications and Supportive Care

6.5.1.1. Tisotumab Vedotin Arm

Premedication for Tisotumab Vedotin

MANDATORY Prophylaxis of Ocular AEs:

In order to reduce the incidence and severity of ocular AEs, all participants randomized to tisotumab vedotin must adhere to the following ocular premedication guidelines:

- 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 participant 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. Cooling pads must cover both eyes (such as an eye mask or cold pack/s) and should 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 participant's eyes during the entire 30 to 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 (ie, 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 participants receiving chemotherapy is recommended. Lubricating eyedrops should be self-administered daily according to the package insert or prescribed instructions from the ophthalmologist.
- It is recommended not to wear contact lenses while being treated with tisotumab vedotin from the first dose until 30 days after the last dose of study drug.

Note that prophylactic premedication does not qualify as an intervention when assessing Common Terminology Criteria for Adverse Events (CTCAE) grading of treatment-emergent ocular AEs.

Supportive Care for Tisotumab Vedotin

Refer to Section 6.6 for additional information regarding dose modification and safety management.

Prophylaxis of alopecia:
DigniCap Scalp Cooling System or similar systems should be considered, if allowed per local guidance, to mitigate chemotherapy-induced hair loss.

Prophylaxis of nausea:
Prophylactic treatment with anti-emetics and anti-pyretics (eg, paracetamol) is strongly suggested for participants experiencing nausea ≥ grade 1 after cycle 1.

Recurrent infusion-related reactions (IRRs):
In case of an IRR ≥ grade 2, the participant should receive premedication prior to the next infusion of tisotumab vedotin (antihistamine, acetaminophen, and/or corticosteroids are recommended).

Recurrent neutropenia:
In case of neutropenic sepsis or neutropenia grade 3 or 4, granulocyte colony-stimulating factor (G-CSF) should be given prophylactically for all subsequent tisotumab vedotin administrations.

6.5.1.2. Chemotherapy Control Arm

Premedication for Chemotherapy Arm

For the chemotherapy arm, administration of premedication should be performed per local labeling or institutional guidelines.

Supportive Care for Chemotherapy Arm

Supportive care for alopecia, IRRs, and bone marrow toxicity (eg, anemia, neutropenia, thrombocytopenia) should be administered per local standards. Anti-emetics should be administered per local standards for ≥ grade 1 nausea or vomiting. Any additional supportive care measures for toxicities identified with the chemotherapies should be administered per local guidelines.

6.5.2. Permitted Concomitant Medications and Therapies

All treatments that the investigator considers necessary for a participant's welfare and according to local labeling or institutional guidelines may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those medications identified as "prohibited" (Section 6.5.3). The participant should be told to notify the study site about any new medications taken after the time of informed consent.

The timing for collection of concomitant medications is specified in Table 1 and Table 3. Concomitant medications administered beyond 30 days after the last dose of study treatment should be recorded for SAEs and AESIs.

6.5.2.1. Permitted Concomitant Medications and Therapies for Tisotumab Vedotin Arm

Anti-coagulation therapy is permitted. Participants being treated with anti-coagulation therapy that requires laboratory assessments for dose titration (warfarin or other vitamin K dependent anticoagulant agents) should have their doses adjusted to target an INR ≤2.5 and must be on a steady dose (no active titration) for at least 4 weeks prior to C1D1. Coagulation parameters, including aPTT and INR, must be measured prior to each infusion of tisotumab vedotin as per the assessment schedule.

6.5.2.2. Permitted Concomitant Therapy for Tisotumab Vedotin Arm Requiring Caution or Action

Drugs and substances known to be strong CYP3A or P-gp inhibitors according to the US FDA's list of drug interactions should be avoided if possible (FDA 2016). Please see https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm for these lists. If administered, the participant should be closely observed for potential adverse reactions.

6.5.2.3. Permitted Concomitant Therapy for the Chemotherapy Arm

For the chemotherapy arm, permitted concomitant medications and therapies should be provided as per local labeling or institutional guidelines.

6.5.3. Prohibited Concomitant Therapy

Participants should be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. Medications specifically prohibited in the

exclusion criteria are not allowed during the study. If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the sponsor. The final decision on any supportive therapy rests with the investigator or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the sponsor, and the participant.

The following is prohibited for participants receiving tisotumab vedotin:

- Chronic prophylactic treatment with acetylsalicylic acid (eg, aspirin) or chronic anti-platelet therapy in combination with any other anti-coagulation therapy.

The following are prohibited for participants receiving tisotumab vedotin or chemotherapy:

- Investigational agents
- Any other anti-cancer therapy, (eg, immunotherapy, monoclonal antibodies, hormonal therapy)
- MMAE-derived drugs
- Radiotherapy (note: radiation therapy of a symptomatic solitary non-target lesion or to the brain may be allowed at the investigator’s discretion)

The following are prohibited for participants receiving chemotherapy:

- Any drugs that are contraindicated for use with the assigned chemotherapy
- Any other anti-cancer therapy that has not been identified as investigator’s choice

6.6. Dose Modification

6.6.1. Dose Modifications for Tisotumab Vedotin

6.6.1.1. Dose Reduction for Tisotumab Vedotin

For participants who do not tolerate the protocol-specified dosing schedule, dose reductions are permitted in order to allow the participant to continue treatment with tisotumab vedotin. Dose reductions must be preapproved by the sponsor’s medical officer unless permitted according to the dose modification guidelines provided below (Section 6.6.2, Table 6).

In case any dose reduction of tisotumab vedotin is needed, the dose must be reduced according to the guidelines provided below (Table 6). Dose reductions below 0.9 mg/kg are not permitted. Thus, if an AE requiring dose reduction recurs after the second dose reduction of tisotumab vedotin, the participant must permanently discontinue tisotumab vedotin treatment.

Table 6: Tisotumab Vedotin Dose Modification Scheme

Previous dose of tisotumab vedotin	Reduced dose of tisotumab vedotin
2.0 mg/kg	1.3 mg/kg
1.3 mg/kg	0.9 mg/kg[a]

a. Dose reductions below 0.9 mg/kg are not permitted.

6.6.1.2. Dose Delay for Tisotumab Vedotin

Any dose delay resulting from AE(s) that delay(s) treatment with tisotumab vedotin for more than 21 days (delay is counted from date of planned dosing) must be approved by the sponsor's medical officer unless allowed according to the mitigation plans specified in the protocol (refer to Section 6.6.2).

For any dose delay due to AEs, dosing with tisotumab vedotin can be resumed immediately after the AE has improved as indicated in the guidance specified in Section 6.6.2. Tisotumab vedotin must be permanently discontinued for any dose delay >6 weeks, (ie, 42 days calculated from the intended day of the next scheduled dose), unless approved by the sponsor.

6.6.2. Dose Modification Guidelines and Preventive Measures for Specific AEs Observed with Tisotumab Vedotin

6.6.2.1. Ocular AEs

The ocular mitigation plan may be modified, by the ophthalmologist or optometrist based on findings on the ocular examination obtained on either baseline or on-treatment examinations. Sponsor consultation is required prior to any modification.

- All participants must adhere to all ocular preventive measures (refer to Section 6.6.2.1.1 and Section 6.5.1.1).
- In case of ocular AEs, participants must be referred to an ophthalmologist or optometrist for prompt ophthalmological evaluation (within approximately 72 hours). The participant should thereafter be followed closely by the ophthalmologist or optometrist until resolution. Topical treatment should be initiated by the ophthalmologist or optometrist according to the treatment guidelines below.
- If ≥3 ocular AEs occur in a participant, sponsor consultation is required to determine if dose modifications or treatment discontinuation is warranted.

Grading: All ocular AEs should be graded according to both:

CTCAE grading system; assessed by the ophthalmologist based on NCI-CTCAE criteria (CTCAE version 5.0). Note that prophylactic premedication does not qualify as an intervention when assessing CTCAE grading of treatment-emergent ocular AEs.

Dose Modification for Ocular AEs (based on CTCAE grading)	
Conjunctivitis	
Conjunctivitis grade 1	Hold dosing until event is managed effectively Continue same dose for next dosing
Conjunctivitis grade 2 first occurrence	Hold dosing until event has improved to ≤ grade 1 Continue same dose for next dosing
Conjunctivitis grade 2 second occurrence	Hold dosing. • If the event resolves (to baseline) within 6 weeks (calculated from the onset date of the second occurrence of the grade 2 event), the participant can resume tisotumab vedotin dosing at a reduced dose according to the dose reduction scheme (Table 6) • If the event does not resolve (to baseline) within 6 weeks, the participant must permanently discontinue tisotumab vedotin treatment
Conjunctivitis grade 2 third occurrence	Permanently discontinue tisotumab vedotin treatment

Conjunctivitis ≥grade 3	Permanently discontinue tisotumab vedotin treatment
Keratitis	
Keratitis grade 1	Hold dosing until event is managed effectively Continue same dose for next dosing
Keratitis grade 2 first occurrence	Hold dosing until event has improved to ≤ grade 1 Reduce next dose according to dose reduction scheme
Keratitis grade 2 second occurrence	Hold dosing until event has improved to ≤ grade 1 Further reduce next dose according to dose reduction scheme
Keratitis grade 2 third occurrence	Permanently discontinue tisotumab vedotin treatment
Keratitis ≥grade 3	Permanently discontinue tisotumab vedotin treatment
Conjunctival ulceration and ophthalmological findings of fluorescent patches	
Any grade first occurrence	Hold dosing until event is managed effectively Reduce next dose according to dose reduction scheme
Any grade ≥second occurrence	If symptoms do not stabilize/improve after dose reduction, the participant must permanently discontinue tisotumab vedotin treatment
Symblepharon	
Any grade	Permanently discontinue tisotumab vedotin treatment
Conjunctival or corneal scarring	
Any grade	Permanently discontinue tisotumab vedotin treatment
All other ocular AEs[a]	
All other ocular AEs grade 1	Hold dosing until event is managed effectively Continue same dose for next dosing
All other ocular AEs grade 2 first occurrence	Hold dosing until event has improved to ≤ grade 1 Continue same dose for next dosing
All other ocular AEs grade 2 second occurrence	Hold dosing. • If the event resolves (to baseline) within 6 weeks (calculated from the onset date of the second occurrence of the grade 2 event), the participant can resume tisotumab vedotin dosing at a reduced dose (according to the dose reduction scheme). • If the event does not resolve (to baseline) within 6 weeks, the participant must permanently discontinue tisotumab vedotin treatment
All other ocular AEs grade 2 third occurrence	Permanently discontinue tisotumab vedotin treatment
All other ocular AEs ≥grade 3	Permanently discontinue tisotumab vedotin treatment

a. Unless more strict mitigation is indicated by sponsor

6.6.2.1.1. Ocular Preventive Measures

In order to prevent ocular AEs, all participants randomized to tisotumab vedotin must adhere to the ocular premedication guidelines specified in Section 6.5.1.1.

6.6.2.1.2. Guidelines for Treatment Prescribed by the Ophthalmologist or Optometrist

Ocular symptom (CTCAE grading)	**Treatment guideline** (The length of treatment is to be decided by the local ophthalmologist)
Conjunctivitis grade 1	Frequent dosing of preservative-free topical steroid drops is recommended.
Conjunctivitis grade 2	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol is recommended.
Conjunctivitis grade 3	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol is recommended.
Keratitis grade 1	Frequent dosing of preservative-free topical steroid drops is recommended.
Keratitis grade 2	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol is recommended.
Conjunctival ulceration: any grade	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol is recommended.

6.6.2.2. Other AEs for Tisotumab Vedotin

Dose Modification Guidelines for Other AEs (based upon CTCAE grading)	
Bleeding events	
• Control vital signs and ensure stabilization of the participant according to local standards. • Prompt evaluation to identify the underlying etiology of the bleeding event. Management should be dictated by the underlying diagnosis. • Control laboratory coagulation and hematologic parameters including prothrombin (PT), aPTT, fibrinogen, platelets, INR, and hemoglobin as soon as possible.	
All participants:	
Any grade pulmonary or CNS hemorrhage	Permanently discontinue tisotumab vedotin treatment.
Hemorrhage (other)[a] ≥grade 4	Permanently discontinue tisotumab vedotin treatment.
Participants <u>not</u> on anti-coagulation therapy:	
Hemorrhage (other)[a] grade 3 first occurrence	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) There is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence. When the above criteria are fulfilled, the participant can resume treatment with tisotumab vedotin at the same dose as prior to the event.
Hemorrhage (other)[a] grade 3 ≥second occurrence	Contact the sponsor's medical officer in order to discuss whether the participant can continue or must permanently discontinue tisotumab vedotin treatment.
Participants on anti-coagulation therapy:	
INR >3.0 with ongoing hemorrhage (other)[a] ≤grade 2	Participants on therapeutic anti-coagulation whose INR is >3.0 prior to infusion of tisotumab vedotin must hold dosing until INR is <3.0. Participants may resume tisotumab vedotin administration immediately after the INR is <3.0. Strongly consider holding anti-coagulation until the above parameters are met.
Hemorrhage (other)[a] ≥grade 3	Hold anti-coagulation therapy. Contact the sponsor's medical officer in order to discuss whether the participant can continue or must permanently discontinue tisotumab vedotin treatment.
INR requirements for participants on anti-coagulants who are not experiencing a bleeding event	
INR >3.0	Participants on warfarin or other vitamin K dependent anticoagulant agents whose INR is >3.0 prior to infusion of tisotumab vedotin must hold dosing until INR is <3.0. Participants may resume tisotumab vedotin administration immediately after the INR is <3.0. Strongly consider holding anti-coagulation until the above parameters are met.

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

Dose Modification Guidelines for Other AEs (based upon CTCAE grading) (cont.)	
Infusion-Related Reactions (IRRs)	
• As a routine precaution, participants enrolled in this study must be monitored during infusion and treated in an area with resuscitation equipment and emergency agents. • All participants should be observed for 2 hours after ending their first infusion of tisotumab vedotin and 15 minutes for all subsequent cycles. • In case any clinically significant IRR is observed during or after the first infusion of tisotumab vedotin or at subsequent treatment cycles, the participant should be observed for 2 hours after ending the administration of tisotumab vedotin 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.	
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 participant should receive premedication (antihistamine, acetaminophen and corticosteroids are recommended) before next infusion.
Grade 3 first 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 participant should receive premedication (antihistamine, acetaminophen, and corticosteroids are recommended) before next infusion.
Grade 3 second 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.
Liver parameters elevated	
Grade 3	Contact the sponsor's medical officer before next dosing of the participant, in order to decide whether next dose of tisotumab vedotin should be reduced, next dosing delayed, or tisotumab vedotin should be permanently discontinued.
≥Grade 4	Permanently discontinue tisotumab vedotin treatment.
Mucositis	
Grade 3	Hold dose until event has improved to ≤ grade 2. Start treatment according to local practice.
≥ Grade 4	Permanently discontinue tisotumab vedotin treatment.
Neutropenia	

Grade 3 or 1st occurrence of grade 4	Hold dosing until event has improved to ≤ grade 2 (including G-CSF administration) G-CSF may be given prophylactically for subsequent tisotumab vedotin administrations.
Grade 4 2nd occurrence	Contact sponsor's Medical Officer in order to discuss dose reduction or discontinuation of tisotumab vedotin.
Peripheral neuropathy (including PTs as: neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy)	
Grade 2 and 3 Initial or worsening of pre-existing condition	Hold dosing until event has improved to ≤ grade 1 Reduce next dose according to dose reduction scheme (Table 6).
≥ Grade 4	Permanently discontinue tisotumab vedotin treatment.

6.6.3. Dose Modifications for the Chemotherapy Control Arm

Dose modifications for the chemotherapy arm should always be performed as per local labeling or institutional guidelines. Appendix 7 (Section 10.7) provides toxicity management recommendations for selected AEs that are characteristic for the investigator's choice chemotherapy agents.

6.7. Intervention after the End of the Study

No interventions are planned after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

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

- Unacceptable AE requiring treatment discontinuation (see Section 8.4)*
- Death
- Pregnancy
- Participant withdrawal of consent from the study
- Participant request to discontinue study treatment*
- Clinical progression*
- Radiographic evidence of disease progression
- Investigator decision
- Other

*Despite treatment discontinuation, imaging should continue to be performed until evidence of radiographic disease progression or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

When a participant discontinues study treatment, they are to remain on study and are to be followed until death, initiation of subsequent therapy, or any other reason listed in Section 7.2.

7.1.1. Summary of Safety Stopping Rules

Tisotumab vedotin treatment must be permanently discontinued in case the participant fulfills any of the below criteria. Treatment discontinuation for the chemotherapy administered in the control arm should be done per local labeling or institutional guidelines.

Tisotumab vedotin discontinuation criteria for ocular AEs:

- Second occurrence of CTCAE grade 2 conjunctivitis that does not resolve to baseline within 6 weeks
- Third occurrence of CTCAE grade 2 conjunctivitis
- First occurrence of CTCAE ≥ grade 3 conjunctivitis
- Third occurrence of CTCAE grade 2 keratitis
- First occurrence of CTCAE ≥ grade 3 keratitis
- Ophthalmological evaluation reveals conjunctival/corneal scarring
- Any grade of symblepharon
- Second occurrence of any grade of fluorescent patches or conjunctival ulceration

- Second occurrence of all other ocular CTCAE grade 2 AEs that does not resolve within 6 weeks
- Third occurrence of all other ocular CTCAE grade 2 AEs
- First occurrence of all other ocular CTCAE ≥ grade 3AEs
- Any dose delay >6 weeks calculated from the intended day of the next scheduled dose, unless approved by the sponsor

Tisotumab vedotin discontinuation criteria for other AEs:

- Any grade pulmonary or CNS hemorrhage
- First occurrence of a ≥ grade 4 hemorrhage (other)
- Second occurrence of a grade 3 IRR (despite premedication)
- First occurrence of a ≥ grade 4 IRR
- First occurrence of mucositis ≥ grade 4
- First occurrence of liver parameter elevated ≥ grade 4
- First occurrence of peripheral neuropathy ≥ grade 4
- Any dose delay > 6 weeks calculated from the intended day of the next scheduled dose, unless approved by the sponsor

7.1.2. End of Treatment Visit

When study treatment is permanently discontinued, investigators are to perform an end of treatment visit. The end of treatment visit should be performed 30 days (±5 days) after the participant has received the last dose of study treatment (Table 1 and Table 3).

7.1.2.1. Post-Study Treatment Anti-Cancer Therapy Status

If a participant initiates a new anti-cancer therapy within 30 days after the last dose of study treatment, the 30-day end of treatment visit should occur before the first dose of the new therapy, if possible. Once new anti-cancer therapy has been initiated, the participant will enter survival follow-up.

7.1.2.2. Survival Follow-up

Information about survival status and initiation of any new anti-cancer therapy should be collected every 60 days (±7 days) (or more frequently around the time of a database lock), beginning from the day of last study treatment dose until death or withdrawal from study. If for any reason a participant enrolled into the study comes off treatment prior to receiving study drug, survival follow-up can be collected from the date of the EOT visit or day of EOT if no visit occurred. Survival follow-up can be performed by telephone contact (the participant or a family member may give the requested information) or during a routine visit, if such a visit is scheduled for other reasons not related to this study. This should be documented in the medical records. Information related to subsequent progression after initiation of new anti-cancer therapy or death from any cause, whichever comes first, is to be collected.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants are to be withdrawn from the study for the following reasons:

- Death
- Lost to follow-up (see Section 7.3)
- Study termination by sponsor
- Participant withdrawal of consent
- Other

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. A participant may choose to discontinue from any future study assessments (eg, dosing, imaging, blood sampling, etc.) but agree to remain in the study and to be followed for survival follow-up, without withdrawal of consent. If a participant withdraws consent from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. Study drug assigned to the withdrawn participant may not be assigned to another participant. Participants who withdraw will not be replaced. The investigator and sponsor will make every effort to ensure participant data are followed for completion of all study safety assessments including end of treatment follow-up and survival follow-up (refer to Table 1 and Table 3) at the time of study discontinuation.

7.2.1. Follow-up for Safety Evaluations

All participants will have safety evaluations at 30 days after the last dose of study treatment at the end of treatment visit (refer to Table 1 and Table 3). Some AEs may be followed beyond this period (refer to Section 8.4.3).

7.3. Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

For participants whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the participant, family, or family physician as agreed in the ICF and by documenting in the source documents steps taken to contact the participant, eg, dates of telephone calls, registered letters, etc. A participant should not be considered lost to follow-up until due diligence has been completed (minimum of 3 documented attempts). Participants lost to follow-up should be recorded as such on the appropriate disposition electronic case report form (eCRF).

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the schedule of activities (SoA) (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Demography and Baseline Assessments

8.1.1. Demographics

Demographic details must be assessed and recorded in the eCRF at screening.

8.1.2. Diagnosis and Disease Status

A participant's history relating to the underlying disease, including primary diagnosis, date of diagnosis, and disease status at study entry, will be recorded at screening.

8.1.3. Medical History

Medical history is defined as all relevant past and all current medical conditions/diseases (besides cervical cancer) occurring prior to first dose (refer to Section 8.4.2 for details on the timing of AE reporting). Medical history includes all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Any abnormalities identified during screening prior to C1D1, including baseline ocular assessment, should be entered into the participant's medical history. Details regarding the cancer for which the participant has enrolled in the study will be recorded separately and not listed as medical history.

8.1.4. Concomitant Medication

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.5.3).

The participant should be told to notify the study site about any new medications they are taking. All medications and significant non-drug therapies (including herbal/natural medications and blood transfusions) administered during the study must be recorded in the eCRF from the time of informed consent and up to 30 days after the last dose of study treatment. Thereafter only new anti-cancer therapy will be collected as noted in Table 1 and Table 3.

8.1.5. Prior Cancer Therapy and Surgery

Administration of prior anti-cancer therapies for treatment of cervical cancer (including surgery, radiotherapy, chemo-radiotherapy, systemic therapy regimens, etc.) from the time of the initial cervical cancer diagnosis until enrollment in this study must be reported in the appropriate section of the eCRF.

8.2. Efficacy Assessments

8.2.1. Tumor Imaging

Tumor images will be reviewed by the local investigator. Images will also be collected for a potential blinded independent central review.

The imaging process is described in a separate imaging guidance document. Tumor imaging should be performed by CT (preferred), unless otherwise indicated in the imaging guidance document. MRI should be used only when CT is contraindicated, for imaging of the CNS, or for certain anatomical regions (see imaging guidance document). The same imaging technique with respect to the modality and use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden. Determination of measurable disease based on RECIST v1.1 will be conducted by the local site investigator during screening for assessment of participant eligibility and during the study for assessment of response.

8.2.1.1. Baseline Imaging Assessments

Baseline imaging assessments will be performed at screening within 28 days of start of treatment (Day -28 to Day -1 prior to C1D1).

Any imaging assessments considered of adequate diagnostic quality already completed during the regular evaluation of the participant within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images.

The following assessments are required at screening:

<u>Contrast-enhanced chest, abdomen, and pelvis CT or MRI scan</u>

All participants will have a contrast-enhanced CT or contrast-enhanced MRI scan of the abdomen and pelvis and a non-contrast CT of the chest.

If a participant is known to have a contraindication to CT IV contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

It is strongly recommended that MRI is used for evaluation of lesion(s) present within an irradiated field. Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy. Biopsy confirmation MAY be considered for either target or non-target lesions if the lesion(s) measures <30 mm or if the treating physician determines it is clinically indicated. If a biopsy is performed on a previously irradiated lesion, an MRI (or CT if MRI is contraindicated) should be obtained

following the biopsy procedure and before the start of treatment for use as the baseline screening exam.

Chest X-rays (CXRs) and ultrasound imaging should not be used to measure tumor lesions.

Chest X-ray

A CXR is acceptable at screening in lieu of a chest CT only if the local standard of care does not support a chest CT and the CXR does not show evidence of metastases. Otherwise, a chest CT is required.

If a baseline CXR shows no evidence of metastatic disease, subsequent imaging should also be performed with CXR; however, a chest CT scan must be obtained upon identification of lesions after baseline.

If a baseline CXR shows evidence of metastatic disease, a CT of the chest must be obtained and followed for progression and response per the imaging schedule defined above.

Brain CT or MRI scan (if clinically indicated)

In order for participants with previously treated brain metastases to be eligible to participate in the study, documented stability by brain imaging over at least 4 weeks is required, and there must be confirmation of no new or enlarging brain metastases within 28 days of the first dose of study treatment. If brain metastases are suspected at screening, brain MRI or CT scans should be completed. A contrast-enhanced brain MRI is preferred; however, if MRI contrast is contraindicated, then an MRI without contrast or CT with/without contrast is acceptable. For any participant with known brain metastases at screening, and who achieves a CR during study treatment, a follow-up brain scan is required for confirmatory assessment of CR.

Whole-body bone scan (if clinically indicated)

For any participant with an elevated screening serum alkaline phosphatase level (1.5×ULN range), bone imaging (eg, bone scan or positron-emission tomography [PET] scan) should be conducted to identify possible bone metastases if clinically suspected. If bone metastases are identified that have not been imaged on the CT/MRI performed for baseline tumor imaging (Section 8.2.1.1), then additional baseline and all subsequent tumor imaging studies must include such lesions in the imaging field. A whole-body bone scan should be performed per institutional standard of care (eg, Tc-99 bone scan, whole body bone MRI, FDG-PET or NaF-PET). Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the investigators, FDG-PET scans may be performed to document disease progression as per RECIST v1.1 (Eisenhauer 2009).

CT or MRI scan of other metastatic sites (if clinically indicated)

If clinically indicated, CT or MRI of other areas (eg, neck) of disease, as appropriate, should be performed.

8.2.1.2. Post baseline imaging assessments

Table 7: Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen, and pelvis CT or MRI (with IV contrast enhancement)	Mandated	Mandated, every 6 weeks (±7 days)
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole-body bone scan	If clinically indicated	If clinically indicated
Localized bone CT or MRI	For any lesions identified on the whole-body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
CT or MRI of other metastatic sites (eg, neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

Note: CXR is acceptable at screening in lieu of a chest CT if the local standard of care does not support a chest CT.

Imaging assessments as described in Table 7 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing. Imaging assessments for response evaluation will be performed every 6 weeks (42±7 days) after screening/baseline during the first 30 weeks, and every 12 weeks (84±7 days) thereafter, or more frequently if clinically indicated. Imaging assessments should be scheduled using the first dosing date as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a participant, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment. Any imaging modalities, if obtained and clinically indicated to assess response or progression, must be entered in the electronic data capture pages for evaluation of response or progression.

Each lesion that is measured at baseline must be measured by the same method and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Objective response (according to RECIST v1.1) should be confirmed by a repeat imaging assessment at least 4 weeks (28 days) after the initial response is recorded. Participants who

obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation is not necessary. In participants who discontinue study treatment without evidence of radiographic disease progression, tumor imaging must be performed until evidence of radiographic disease progression or until the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

8.2.2. Survival Status

Survival status will be assessed every 60 days (±7 days) beginning from the day of the last dose of study treatment until the participant withdrawals consent or death, whichever occurs first. Survival status may be requested more frequently around the time of a database lock. This information can be given by the participant or a family member. Information may also be obtained by any mechanism allowed per applicable regulations, such as telephone, email, public information, visit, or other.

8.3. Safety Assessments

8.3.1. Physical Examination

A complete physical examination is required at screening and includes, at a minimum, general appearance of the following body systems: lymph node regions, mouth and throat, lungs, cardiovascular, abdomen, extremities (including muscular-skeletal system), neurological system, and skin. Clinically significant abnormal findings should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs. During the treatment phase, a targeted/directed physical examination will be performed as specified in Table 1 and Table 3. Targeted examination includes, at a minimum, the following body systems: eyes; ear, nose, and throat; cardiovascular; abdominal and neurological examination.

Body Measurements

Height (measured at screening only) and body weight should be measured as indicated in Table 1 and Table 3. The participant's body weight should be measured and used to calculate the dose of study drug for infusion. If body weight is measured ≤7 days before the day of the planned study treatment, this result can be used for calculation of dose.

8.3.2. Vital Signs

Vital signs (including temperature, blood pressure, respiratory rate, and heart rate) are to be measured according to Table 1 and Table 3. The participant should be resting for ≥10 minutes before vital signs are measured. Temperature should be measured according to local practice. Within each visit, preferably the same equipment shall be used for vital sign measurements. On infusion days, vital signs should be assessed before the infusion start.

8.3.3. Electrocardiograms

For all participants, one 12-lead electrocardiogram (ECG) will be performed at screening, at the end of treatment visit, and as clinically indicated during the treatment period. All participants

should be resting for ≥10 minutes prior to obtaining the ECG. In case any irregularity (eg, vomiting or cough) occurs during the recording of the ECG, the ECG should be repeated. The ECG recordings should be locally evaluated by investigator (the investigator may delegate this task to a cardiologist, if applicable) in order to exclude any safety concerns.

8.3.4. ECOG Performance Status

ECOG performance status will be assessed by the investigator as indicated in Table 1 and Table 3 and scored per Table 8.

Table 8: ECOG Performance Status

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

8.3.5. Eye Examination and Ocular Assessment

Eye examination should be assessed by investigator as indicated in Table 1 (every visit except survival follow-up visit). The eye examination should include a visual inspection of the eye orbit and conjunctiva and control of normal eye movement. The participant should furthermore be asked about any ocular symptoms (eg, itchy eyes, sticky eyelids, eye secretion, blurry vision, etc.).

An ocular assessment should be performed by an optometrist or ophthalmologist at screening for baseline evaluation, as indicated in Table 1 and Table 3. This assessment may also be performed as needed at unscheduled visits by the treating physician or delegate. The following assessments should be performed: visual acuity, Schirmer's test, slit lamp, inspections of the conjunctivas and corneas including staining, intraocular pressure, and fundoscopy. A visual inspection of the eye orbit and conjunctiva and control of normal eye movement should also be performed. Clinically significant abnormal findings at baseline should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

Participants should be informed to contact their investigator or delegate immediately in case of any ocular symptoms appearing between tisotumab vedotin administration days and should be referred for a prompt ophthalmologist or optometrist evaluation (within 72 hours).

8.3.6. Clinical Laboratory Assessments

Laboratory assessments detailed in Table 9 should be obtained according to the schedule of assessments outlined in Table 1 and Table 3. All clinical laboratory tests will be performed

locally. This testing will include institutional standard tests for evaluating safety and making clinical decisions. Results of clinical laboratory tests are to be submitted to the central laboratory.

Laboratory tests for screening should be performed ≤7 days prior to the first dose of study treatment. After Cycle 1, pre-dose laboratory procedures can be conducted ≤72 hours prior to dosing. Results will be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of study treatment.

Additional local laboratory assessments not included in the assessment schedule, eg, needed for dosing decision, should be obtained and collected as required according to local labels and guidelines for topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed and results submitted to the central laboratory. Also, unscheduled laboratory assessments may be obtained at the discretion of the investigator, eg, to be used as supportive information for an AE or for dose modifications or delays of the study treatment. For details on AE reporting of laboratory test abnormalities, refer to Section 8.4.2.

Table 9: Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Hematocrit	Red blood cell indices: MCH MCHC MCV %Reticulocytes	WBC count with differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils
	Hemoglobin		
	Platelet count		
	RBC count		
Coagulation factors	aPTT	INR	Fibrinogen
Biochemistry	ALT	Calcium	Magnesium
	Albumin	C-reactive Protein	Sodium
	Alkaline phosphatase	Creatinine (GFR calculation)	Total and direct bilirubin
	AST	Glucose	Uric acid
	blood urea nitrogen	Lactate dehydrogenase	Potassium
eGFR	Calculated eGFR (MDRD formula)		
Other Screening Tests	HBsAg/HBV DNA, or HCVAb or RNA (where applicable)		
Pregnancy Test[a]	Serum or urine beta-human chorionic gonadotropin[b]		

a. For participants of reproductive potential (see Section 10.4)
b. Serum beta-hCG is required at screening for eligibility. Thereafter, serum or urine can be used unless urine pregnancy results cannot be confirmed as negative, or if required as per local regulations where applicable.

8.4. Adverse Events and Serious Adverse Events

8.4.1. Adverse Event Definitions

8.4.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a clinical study participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

8.4.1.2. Definition of Serious Adverse Event

An SAE is defined as an AE that meets one of the following criteria:

- Is fatal or life-threatening[1]
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgment must be exercised in deciding whether an AE is “medically important”.
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]

1. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
2. Hospitalizations for the following reasons should not be reported as SAEs:
   - Routine treatment or monitoring of the underlying disease, not associated with any deterioration in condition
   - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF
   - Social reasons and respite care in the absence of any deterioration in the participant’s general condition
   - Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE

8.4.1.3. Definition of AEs of Special Interest for Tisotumab Vedotin

AESIs are defined as events (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program. Such events may require further investigation in order to characterize and understand them. Some AESIs require immediate reporting, as described in Section 8.4.2. AESIs are defined on the basis of an ongoing review of the safety data. The following AESIs for tisotumab vedotin are discussed further in the Investigator's Brochure:

- Ocular AEs
- Bleeding AEs
- Peripheral neuropathy AEs

8.4.2. Adverse Event Reporting

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

The safety reporting period for all AEs is from study Day 1 (predose) through the EOT visit or 30 days after the last drug administration, whichever is later. AEs that occur after the ICF is signed and prior to first study treatment dose should be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy or CT scan), including washout or discontinuation of prior medications. Any medical condition (signs, symptoms, and diagnosis) occurring prior to first study treatment dose should be recorded as medical history in the "Medical History & Pre-existing Conditions" form. Any medical history condition that worsens after the first dose of study treatment will be recorded as an AE.

The following AEs must be reported to the sponsor within 24 hours:

- All SAEs
- All Ocular AEs regardless of grade
- All events of overdose and/or medication errors with tisotumab vedotin whether associated with an AE or not. All events of overdose and/or medication errors with the comparator chemotherapy, only if associated with an AE
- Any event of pregnancy (regardless of treatment arm)

Completed safety reporting documents must be forwarded to the sponsor within 24 hours following one of these events:

a. the participant visit at which such AE was reported, noted, or recognized
b. the principal investigator's or any investigator personnel's receipt of the test results
c. other information at, or from which, such development was reported, noted, or recognized.

Study sites should make every effort to respond to follow-up queries from sponsor within 3 working days.

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.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

All AEs must be followed until they are resolved or until the end of treatment visit, whichever occurs first. However, AESIs qualifying for safety reporting and all SAEs (independent of causality) still ongoing after the end of treatment visit should be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved. Only SAEs judged by the investigator as related to study treatment should be reported after the 30-day end of treatment visit.

Assessment of all peripheral neuropathy cases (regardless of meeting criteria for safety reporting) will be performed every 60 days (by telephone contact) from the time of treatment discontinuation until one of the following criteria are met:

- The event returns to baseline or to grade 1
- The participant changes to another chemotherapeutic agent with known neurologic toxicity
- The participant is considered lost to follow-up

8.4.4. Diagnosis

The diagnosis/underlying cause of an AE should be recorded rather than symptoms of the AE. If no diagnosis is available, each sign and symptom must be recorded as individual AEs.

8.4.5. Suspected Unexpected Serious Adverse Reactions

The sponsor will ensure that all relevant information about serious unexpected suspected adverse reactions (SUSARs) is recorded and reported as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge by the sponsor or designee, to the competent regulatory authorities, and/or to the ethics committee according to the applicable local regulatory requirements. Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional 8 days.

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

8.4.6. Pregnancy

Any pregnancy in a study participant must be reported to the sponsor within 24 hours of learning of its occurrence. Pregnant study participants must immediately permanently discontinue trial treatment. The pregnancy should be followed up to determine outcome (including premature termination) and status of mother and child. The child should be followed up to approximately 6 months of age. Pregnancy complications and elective terminations for medical reasons must be

reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to study treatment must be promptly reported to the sponsor.

8.4.7. Pre-existing Condition

In this study, a pre-existing condition (ie, a disorder present before the AE reporting period has started and noted on the Medical History & Pre-existing Conditions form) should not be reported as an AE. If a pre-existing condition worsens during the AE reporting period, the event must be reported as an AE.

8.4.8. Disease Progression or Death

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.

All deaths within 30 days of last dose, except death caused by disease progression, should be reported as SAEs.

8.4.9. Unrelated Procedures

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

8.4.10. Laboratory Test Abnormalities

Any laboratory abnormality that induces clinical signs or symptoms, requires concomitant therapy, or requires changes in study treatment must be reported as an AE. The following laboratory test result abnormalities should be captured as AEs or SAEs, as appropriate:

- Any laboratory test result abnormality that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that requires the participant to have study drug discontinued or interrupted
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy

Whenever possible, a diagnosis, rather than a symptom, should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs must be followed until they have returned to normal or an adequate explanation of the abnormality is found. When

an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

Note: A CTCAE grade 3 or 4 laboratory value abnormality does not automatically indicate an SAE.

8.4.11. Information About Infusion-Related Reactions

For all AEs with onset during or <24 hours after infusion of study drug, the investigator must assess whether the AE is considered caused by the infusion (ie, considered an IRR).

8.5. Treatment of Overdose

8.5.1. Overdose and Medication Errors

For tisotumab vedotin dose administration, please refer to Section 6.1.1. For the purposes of this study, an overdose is defined as >10% of the prescribed tisotumab vedotin dose or ≥20% of any prescribed chemotherapy dose. No specific information is available on the treatment of overdose of tisotumab vedotin. There is currently no known antidote for an overdose of tisotumab vedotin.

In the event of overdose, tisotumab vedotin or chemotherapy should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. Notify the sponsor's medical monitor as soon as they become aware of the overdose, to relay details of the overdose (e.g., exact amount of tisotumab vedotin administered, participant weight) and AEs, if any.

If an AE is associated with ("results from") the overdose of tisotumab vedotin, the AE should be reported as an SAE, even if no other seriousness criteria are met. If a dose of tisotumab vedotin meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious AE, using the terminology "accidental or intentional overdose without adverse effect." All reports of overdose with and without an AE must be reported within 24 hours to the sponsor.

8.6. Pharmacokinetics

Blood samples for assessment of tisotumab vedotin and MMAE will be drawn in accordance with the PK assessment schedule (refer to Table 2). Three assays will be performed:

- Detection of tisotumab vedotin (ie, conjugated antibody only)
- Detection of total antibody (ie, conjugated and unconjugated antibody)
- Detection of free MMAE in circulation
- Samples will be used to evaluate the PK of tisotumab vedotin. Remaining samples collected for analyses of tisotumab vedotin plasma concentration may also be used to evaluate other safety, efficacy, or biomarker laboratory parameters.

Note: Sites will be notified if prospective PK blood sample collection is no longer required during the course of the study.

8.7. Biomarkers

Exploratory biomarker assessments may be performed on tumor tissues and/or whole blood samples, to expand on the understanding of pharmacodynamic effects and the mechanism of action of tisotumab vedotin, assess potential predictors of participant response to tisotumab vedotin, or further the understanding of TF biology and cervical cancer. Samples for exploratory biomarkers will be collected at protocol-specific time points as specified in Table 1 and Table 3. Biomarker assessments will not be used for participant selection.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.7.1. Biomarker Assessments in Blood and Tumor Samples

Biomarker assays may be performed on blood samples to address whether changes in circulating tumor DNA correlate with patient response and level of disease.

Tissue biopsies may be assessed for specific pharmacodynamic, predictive, and prognostic biomarkers in the tumor. To characterize the malignancy and response to study treatment, biomarker assessments in tumor biospecimens may include measurements of tisotumab vedotin and its potential metabolites as well as characterization of the tumor microenvironment, drug target(s), tumor subtyping, profiling of somatic mutations and/or gene expression.

Biomarker assessments may include:

- **Expression of TF protein.** TF expression in the tumor will be explored in relation to clinical response. Other proteins related to tisotumab vedotin mechanism of action and cervical cancer (PD-L1 or other proteins) may also be explored in tumor biopsies by IHC or similar methods.
- **Tumor messenger RNA expression**. RNA sequencing may be performed on tumor biopsies to determine TF RNA expression levels, and to evaluate expression of other genes associated with cervical cancer biology, response to tisotumab vedotin (eg, MDR1, MDR6), or markers of the immune microenvironment (eg PD-1, PD-L1, CD8).
- **Tumor DNA sequencing.** Next generation sequencing (NGS) may be performed to evaluate DNA mutations, copy number variations, microsatellite instability, insertions, deletions, or rearrangements in genes associated with the mechanism of action of tisotumab vedotin or cervical cancer biology.

8.7.2. Tumor Tissue Sample Collection

Samples for biomarker analyses will be collected as specified in Table 1 and Table 3. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

For the purposes of screening, the most recent archival tumor biopsy should be collected for biomarker analyses, preferentially within the last 2 years. If an adequate archival tumor biopsy less than 2 years old is not available, a fresh tumor biopsy should be collected before initiation of study treatment, if clinically feasible. If a fresh biopsy cannot be collected, the most recent archival tumor sample may be submitted, even if obtained more than 2 years prior to participant enrollment. Note that no tumor biopsy sample is required to be provided if the subject fails screening.

An optional fresh biopsy collected at time of radiographic disease progression may be provided for biomarker analyses, if clinically feasible and if the participant provides consent for this procedure.

If a tumor biopsy is collected per standard of care while the participant is on study (until treatment discontinuation), the FFPE block or unstained slides may be provided for biomarker analyses, if the participant provides consent for this procedure.

Core needle and excisional biopsies, or resected tissues, formalin fixed and paraffin embedded, are acceptable. FFPE blocks are preferred to unstained slides. If unstained slides are provided, freshly cut serial sections are requested. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

If it is determined at any time before study completion that additional material is needed from a FFPE tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material from existing samples. Also, based on emerging scientific evidence relating to a potential correlation between a biomarker and treatment efficacy or safety, the sponsor may request additional material from previously collected tumor samples.

8.7.3. DNA/RNA Research

DNA/RNA samples from the tumor may be analyzed to assess gene expression levels, mutations, copy number variations, microsatellite instability, insertions, deletions, and rearrangements in genes as described in previous biomarker sections.

DNA/RNA samples may be used for research related to tisotumab vedotin or cervical cancer.

8.7.4. Patient Reported Outcomes

The following HRQOL questionnaires will be completed as described in Table 1 and Table 3. It is strongly recommended that the questionnaires be completed by the participant first upon arrival for a visit (ie, before any disease/treatment dialog with study nurse/treating physician or initiation of other preparations for the study treatment).

EQ-5D-5L

EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of HRQOL that can be used in a wide range of health conditions and treatments (Herdman 2011) (Rabin 2001). The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the participant's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the participant's own judgment. The scores on these 5 dimensions can be presented as a health profile or can be

converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

EORTC-QLQ-C30

The QLQ-C30 is a validated questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) to assess the quality of life of participants with cancer in multicultural clinical research settings (Aaronson 1993).

EORTC-QLQ-CX24

The EORTC-QLQ-CX24 is a validated questionnaire developed by the EORTC to assess the quality of life in patients who are treated for cervical cancer both in clinical studies and in clinical practice (Greimel 2006).

8.8. Immunogenicity Assessments

8.8.1. Evaluations

Venous blood samples will be drawn for central analysis of ADAs at the time points shown in Table 2. Samples collected for ADA to tisotumab vedotin may also be used to evaluate safety, efficacy, or biomarker laboratory parameters to address concerns arising during the study.

8.8.2. Immunogenicity Assessments

Antibodies to tisotumab vedotin will be evaluated in serum samples collected from all participants according to the visit schedule (Table 2).

Serum samples will be screened for antibodies binding to tisotumab vedotin and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to tisotumab vedotin or further characterize the immunogenicity of tisotumab vedotin.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The overall type I error for this study is controlled at 5% (2-sided) for the statistical hypotheses on the primary endpoint, OS, and the key secondary endpoints, PFS and ORR, by using a hierarchical group sequential procedure (GSP) (Maurer 2013). One interim analysis (IA) and one final analysis (FA) are planned, and the timing of the analyses will be determined by the OS endpoint.

9.2. Sample Size Determination

Approximately 482 participants will be randomized in a 1:1 ratio to one of the 2 study arms. No crossover between treatment arms is permitted.

This sample size is determined to provide sufficient power to demonstrate superiority of the tisotumab vedotin arm against the control arm based on the primary endpoint OS. Specifically, this sample size, with a total number of approximately 336 OS events, provides an overall power of 90% for the hypothesis testing on OS at a 2-sided 5% significance level to detect an HR $\neq 1$ when the true HR is 0.7, with the following assumptions:

- median OS of 12.9 months in the tisotumab vedotin arm
- median OS of 9 months in the chemotherapy arm
- drop-out rate of 5% per year
- an IA at approximately 75% (252) of the total number of OS events using the Lan deMets (O'Brien Fleming) boundary (Lan 1983)
- accrual duration of approximately 23 months with at least 12 months of follow-up
- 1:1 randomization ratio

The IA and FA on OS are estimated to occur at approximately 27 and 35 months after the first participant is randomized into the study.

At the OS IA and FA, it is estimated that the number of PFS events will be approximately 413 and 457, respectively, which will provide an overall power of 95% at a 2-sided 5% level of significance assuming an HR of 0.7 with a median PFS of 4.3 months in the tisotumab vedotin arm and a median PFS of 3 months in the control arm.

For ORR, it is estimated that all 482 participants will be fully randomized into the study, based on the assumed accrual, and have at least 2 post-baseline scans at the OS IA and FA timings. This provides an overall power of approximately 99% at a 2-sided 5% level of significance assuming an ORR of 25% for the tisotumab vedotin arm and a 10% ORR for the control arm.

9.3. Populations for Analyses

Intent-to-treat (ITT) analysis set: This analysis set includes all participants who are randomized into the study. Participants will be included in the treatment group assigned at randomization regardless of the actual treatment received. The primary analysis of the efficacy endpoints will

be based on the ITT analysis set. Demographics and baseline characteristics will also be summarized on the ITT analyses set.

Safety analysis set: This analysis set includes all randomized participants who received any amount of the study treatment. Participants will be evaluated by the treatment actually received. Analyses on treatment exposure and safety will be based on the safety analysis set.

Additional analysis sets may be defined in the Statistical Analysis Plan (SAP).

9.4. General Considerations

The SAP will be finalized prior to the database lock for primary analyses, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses on the main study endpoints including primary and key secondary endpoints.

9.4.1. Responsibility for Analyses/In-house Blinding

The statistical analysis of the data from this study is the responsibility of the sponsor.

The randomization list will be prepared by the RTSM system vendor. Although this is an open label study, to maintain trial integrity, analyses or summaries by randomized treatment or actual treatment assignment will be limited and documented while the study is ongoing and before the database lock for primary analyses.

Results of the planned OS, PFS, and ORR interim analyses will be provided to the IDMC by an external independent vendor. Additional details will be provided in a separate document.

9.5. Efficacy Analyses

The primary analyses on efficacy endpoints will be analyzed using the ITT analysis set. Stratified primary analyses will use stratification factors (ECOG, prior bevacizumab, and prior anti-PD-[L]1 therapy) with values as employed in the randomization. The stratification factor of region will not be included in the stratified primary analyses to reduce sparse strata.

9.5.1. Overall Survival

OS is defined as the time from the date of randomization to the date of death due to any cause. OS is the primary endpoint of this trial.

The difference in OS between the treatment and control arms will be assessed by the stratified log-rank test. The 2-sided p-value corresponding to the test of superiority of tisotumab vedotin over chemotherapy (control) will be presented. The estimated HR and its 95% CI from the stratified Cox model will be presented. The median OS will be estimated using the Kaplan-Meier (KM) method and will be presented along with estimated KM curves and the corresponding 95% CI by treatment arm.

In the absence of confirmation of death, survival time will be censored at the last date the participant is known to be alive.

9.5.2. Progression-Free Survival Assessed per Investigator

PFS per investigator is defined as the time from the date of randomization to the first documentation of disease progression per RECIST v.1.1 by the investigator, or to date of death due to any cause, whichever occurs earlier.

PFS will be analyzed using the same methods as described for the primary analyses on OS. In the primary analysis on PFS, participants without evidence of radiographic disease progression or death will be censored at the date of the last adequate tumor assessment prior to data cut-off date or the start of new anti-cancer therapy. Participants with disease progression or death that occur after 2 or more missed scans would be censored at the last adequate tumor assessment prior to the missed scans. Participants without post-baseline scan data would be censored at the day of randomization.

9.5.3. Confirmed Objective Response Rate as Assessed by Investigator

Confirmed objective response rate is defined as the proportion of participants with a confirmed CR or partial response (PR) per RECIST v.1.1.

ORR will be analyzed using a Cochran-Mantel-Haenszel chi-squared test. The common odds ratio across strata will be estimated with its 95% CI and 2-sided p-value for testing of superiority of tisotumab vedotin over chemotherapy.

In the primary analysis of ORR, participants without at least two post-baseline tumor assessments will be considered to be non-responders.

9.5.4. Health-related Quality of Life (HRQOL)

Results of the EQ-5D-5L index based on the UK Value Set, EQ-5D VAS, EORTC-QLQ-C30, and EORTC-QLQ-CX24 will be summarized. Longitudinal and descriptive data analysis will be used to evaluate patient-reported outcomes. Further details on these analyses will be provided in the statistical analysis plan.

9.5.5. Duration of Response and Time to Response

DOR and TTR will be summarized descriptively by treatment group using the Kaplan-Meier approach. Only participants with a confirmed CR or PR will be included in these analyses.

9.5.6. Exploratory Analyses

The relationship between TF expression and efficacy endpoints may be explored. Relationships and associated data that are determined to be of interest will be summarized. Biomarker data, PK, and ADA incidence will be summarized descriptively. Details will be described separately.

9.5.7. Testing Strategy

Hypothesis testing will be performed on the primary endpoint OS and two key secondary efficacy endpoints, PFS and ORR, while controlling the overall Type I error rate of 5% (2-sided) using a hierarchical approach with group sequential testing (Maurer 2013).

The endpoints are tested in the hierarchical order as follows: OS first, then PFS, and finally ORR. Hypothesis testing starts with OS and will only proceed to the hypothesis testing on the

next endpoint, PFS, when the efficacy boundary is crossed for OS at the first time (IA or FA). Similarly, the hypothesis testing on ORR will only occur after the efficacy boundary is crossed for PFS.

For OS, the Lan DeMets (O'Brien-Fleming) spending function will be used (Lan 1983). With approximately 252 and 336 events estimated to occur at the IA and FA respectively, the OS will be tested at a 2-sided nominal 0.019/0.044 level at the IA/FA corresponding to a HR boundary of 0.75/0.80.

For PFS, the Lan DeMets (Pocock) spending function will be used (Lan 1983). With approximately 413 and 457 events estimated to occur at the OS IA and FA respectively, the PFS will be tested at a 2-sided nominal 0.047/0.025 level at the IA/FA corresponding to an HR boundary of 0.822/0.811.

For ORR, it is estimated that all 482 participants will be fully randomized into the study and have at least two post-baseline scans by the OS IA at 27 months. The ORR will be tested at 2-sided 5% level corresponding to an odds ratio boundary of 1.67.

For hypothesis testing on all endpoints, the actual nominal significance level to be applied will be adjusted to reflect the actual number of events realized at the time of the IA/FA using the specified spending function for each endpoint. The overall type 1 error for the 3 key endpoints, OS, PFS, and ORR, is controlled at a 2-sided 5% level using the approach of Maurer and Bretz (Maurer 2013).

9.6. Safety Analyses

Safety analyses will be performed on the safety analysis set.

9.6.1. AEs

An overview of AEs will provide a tabulation of the number and incidence of all treatment-emergent adverse events (TEAEs), treatment-related TEAEs, grade 3 and higher TEAEs, treatment-emergent SAEs, treatment-related treatment-emergent SAEs, deaths, TEAEs leading to dose modification, and TEAEs leading to study treatment discontinuation. A TEAE is defined as a newly occurring or worsening AE after the first dose of study treatment and with onset date on or before 30 days after the last dose of study treatment.

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), system organ class, preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one participant, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to discontinuation of study drug will be summarized and listed in the same manner.

The following groups of TEAEs will be summarized:

- All TEAEs
- Grade 3 to 5 TEAEs
- Treatment-emergent SAEs
- Treatment-related TEAEs

- Treatment-related grade 3 to 5 TEAEs
- Treatment-related treatment-emergent SAEs
- TEAEs leading to dose reduction
- TEAEs leading to dose interruption
- TEAEs leading to dose delay
- TEAEs leading to study drug discontinuation
- Grade 5 TEAEs
- Treatment-emergent AESIs
- Treatment-emergent ocular AEs
- Treatment-emergent bleeding AEs
- Treatment-emergent peripheral neuropathy AEs

Analyses of AEs will be summarized descriptively. Details will be specified in the SAP.

9.6.2. Safety Laboratory Tests, Vital Signs, and ECG Parameters

Continuous measures such as safety laboratory tests and vital signs will be summarized descriptively. Summary statistics for baseline, on-treatment, and change from baseline values will be summarized by treatment group. For safety laboratory parameters, shift tables from baseline based on CTCAE grading will be provided. For 12-lead ECG parameters, only a listing will be generated.

9.7. Interim Analyses

One interim efficacy analysis is planned when approximately 252 (75%) of the total expected 336 OS events occur. The IDMC will evaluate the overall safety and efficacy data at the interim analysis to make recommendations regarding whether to terminate or continue the trial. Overall type I error for OS will be controlled using the O'Brien-Fleming spending function (Lan 1983). More details regarding the interim analysis will be described in the SAP.

9.8. Trial Governance and Oversight

9.8.1. Independent Data Monitoring Committee (IDMC)

An IDMC, consisting of members who are external and independent of the sponsor study team, will be formed to monitor the safety of participants participating in this study on a periodic basis, review safety and efficacy data from this study as per planned analyses, and make recommendations to the sponsor. The IDMC will consist of a minimum of 3 physicians with appropriate disease area qualifications and a statistician who will be a non-voting member of the committee.

Additional details on the IDMC will be described in a separate IDMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve(s) only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see contact information page[s] provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

10.1.2. Regulatory Approval/Notification

This protocol and any amendments must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A trial may not be initiated until all local regulatory requirements are met.

10.1.3. Participant Identification, Enrollment, and Screening Logs

The investigator agrees to assign a unique participant identification to protect the participant's identity and to permit easy identification of each participant during and after the trial. All reports and communications relating to the trial will identify participants by the unique participant identifiers and year of birth or age.

The investigator must complete a participant screening and enrollment log, which reports on all participants who consent to be on trial, those who are screened, screen failures, and those who meet eligibility for inclusion in the trial. The participant identification log will be treated as confidential and will be filed by the investigator in the site file. The screening and enrollment logs will be reviewed by the sponsor or designee for completeness.

10.1.3.1. Participant Identification Card

After signing the ICF, it is recommended that all participants should be given participant identification cards by the site identifying them as participants in a clinical trial. The card should

contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency.

10.1.4. Ethics

10.1.4.1. Trial-Specific Design Considerations

Potential participants will be fully informed of the risks and requirements of the trial and, during the trial, participants will be given any new information that may affect their decision to continue participation. Only participants who are fully able to understand the risks, benefits, and potential AEs of the trial, and provide their consent voluntarily, will be enrolled.

The total blood volume to be collected is considered to be within the normal range allowed for this participant population over the time frame of the trial.

10.1.4.2. Regulatory Ethics Compliance

Investigator Responsibilities
The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

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. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the trial data are credible.

Independent Ethics Committee or Institutional Review Board
This trial will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data, or trial conduct), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this written approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of samples for exploratory and DNA/RNA research and for the corresponding ICF must be obtained from the IEC/IRB as required by local regulations. Approval for the protocol can be obtained independent of this research component.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and written approval before implementation of the change(s) unless the amendment is issued to eliminate immediate hazards to trial participants.

Where applicable, interim reports on the trial and/or review(s) of trial progress will be submitted by the investigator to the IEC/IRB at intervals stipulated in its guidelines.

At the end of the trial, the investigator (or sponsor where required) will notify the IEC/IRB about the trial completion.

10.1.4.3. Return of Exploratory Research Data to Participants and Investigators

Exploratory biomarker research is not conducted under standards appropriate for the return of data to participants or investigators. In addition, the sponsor cannot make decisions as to the clinical significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.1.5. Biospecimen Repository

In the US only, for participants who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seagen Inc 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.

10.1.6. Regulatory and Ethical Considerations/Statement of Compliance

- This study will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.
- The investigator will be responsible for the following:
- Providing the following to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/IEC:
  - Protocol and amendments
  - Informed consent document and updates

  - 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
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The investigator must provide the following documentation to the sponsor or its designee:
- The IRB/IEC periodic (eg, 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.

10.1.7. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10.1.8. 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.

10.1.9. 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.

10.1.10. Informed Consent Process

The investigator is responsible for presenting the risks and benefits of study participation to the participant in simple terms using the IRB/IEC approved informed consent document and for ensuring participants 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 participant, 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 participant who is unable to provide informed consent at study entry (if applicable), but the participant is later able

to provide informed consent, the investigator must obtain written informed consent from the participant.

The ICFs that are used must be approved by the reviewing IEC/IRB and be in a language that the participant can read and understand. The ICF should be in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines, applicable regulatory requirements, and sponsor policy.

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without justifying the reason. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of their disease. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable laws or regulations. By signing the ICF, the participant is authorizing such access and agrees to allow their trial physician to re-contact the participant for the purpose of obtaining consent for additional safety evaluations, including scans, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Where required, a separate consent will be used for long-term retention of remaining samples for additional exploratory research (Refer to Section 10.1.5).

10.1.11. Data Protection

10.1.11.1. 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 participant medical records in the participant 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 participant medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the participant 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, case report forms 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 participant 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.

10.1.12. Data Quality Assurance

10.1.12.1. Monitoring

The sponsor or delegate will use a combination of remote and on-site monitoring to monitor this trial. The sponsor or delegate will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial-site visit log that will be kept at the trial-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the trial-site personnel. The sponsor expects that, during monitoring visits, the relevant trial-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will speak with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, trial-site personnel will be available to provide an update on the progress of the trial at the site.

10.1.13. Source Documents

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: participant identification, eligibility, and trial identification; trial discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; trial drug administration information; and date of trial completion and reason for early discontinuation of trial drug or withdrawal from the trial, if applicable. In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a participant should be consistent with that commonly recorded at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial and will be described in the monitoring guidelines (or other equivalent document).

10.1.14. Study and Site Start and Closure

The sponsor reserves the right to close a site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Sites will be closed upon trial completion.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for early closure of a site by the sponsor or investigator include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or ICH Good Clinical Practice guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further tisotumab vedotin development
- If the development of the tisotumab vedotin is discontinued, or study closure is necessary, the sponsor will ensure provisioning of post-study treatment for ongoing study participants

10.1.15. Publication Policy

The publication policy for clinical data from this trial can be found within the Clinical Trial Agreement.

10.1.16. Registration of Clinical Trials and Disclosure of Results

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.

10.2. APPENDIX 2: Clinical Laboratory Tests

Please refer to Section 8.3.6, Table 1 and Table 3.

10.3. APPENDIX 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Please refer to Section 8.4.

10.4. APPENDIX 4: Definition of Reproductive Potential and Guidance on Contraception

In this study, participants are considered to have reproductive potential, UNLESS they are post-menopausal or permanently sterile.

- A post-menopausal state is defined as no menses in participants >45 years of age, for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range should be used to confirm a post-menopausal state in participants not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

All participants must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the study and for 6 months after receiving the last dose of study treatment.

Participants of reproductive potential must agree to use adequate contraception during and for 6 months after the last study treatment administration. Adequate contraception is defined as highly effective methods of contraception (Table 10). Birth control methods are considered highly effective if they have a failure rate of <1% per year, when used consistently and correctly.

Table 10: Acceptable Methods of Contraception

Participants who are of childbearing potential[a] who are sexually active in a way that could lead to pregnancy may choose to use complete abstinence*, if consistent with the participant's preferred lifestyle, OR any TWO of the following methods:

- Hormonal methods of contraception associated with inhibition of ovulation
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- A barrier method (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)

*Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug

a. A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, 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 years in the absence of other biological, physiological, or pharmacological causes.

Unacceptable Methods of Contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms

Tables adapted from "Recommendations related to contraception and pregnancy testing in clinical trials." advisory non-binding guidance represented at the Clinical Trials Facilitation Group meeting, Rome 2014. (UK MHRA 2014).

10.5. APPENDIX 5: Genetics

Not applicable.

10.6. APPENDIX 6: Liver Safety: 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 (ie, 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. During this investigation, study drug should be withheld.

10.7. APPENDIX 7: Dose Modifications for the Chemotherapy Arm

Dose modifications for the chemotherapy arm should always be performed as per local labeling or institutional guidelines. The following section provides toxicity management recommendations for selected AEs that are characteristic for the investigator's choice chemotherapy agents. For other chemotherapy-related AEs that are not specifically addressed in the following sections, the general approach for ≥ grade 3 TEAEs is to hold chemotherapy until resolution of the event to ≤ grade 1 or baseline, and to reduce by 1 dose level on resumption of treatment.

The starting doses specified in Section 6.1.2 should not be modified. Treatment may be delayed to allow for resolution of toxicity to pretreatment, baseline levels. The treating investigator should contact the sponsor to discuss the case of any participant whose treatment has been delayed beyond what is specified in local labeling or institutional guidelines.

Dose adjustments at the start of a subsequent cycle should be based on nadir observed hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, participants may be retreated using guidelines in the following subsections. Missed doses of chemotherapy will not be made up.

10.7.1. Recommended Dose Modifications for Topotecan

The starting dose for topotecan is 1.0 mg/m^2 or 1.25 mg/m^2 × 5 days, every 21 days.

Toxicity	Dose Modification
ANC ≤1000/mm^3 or Platelet count of ≤100,000/mm^3 or Hemoglobin <9.0 g/dL or Serum creatinine >1.5 mg/dL	Delay next cycle of topotecan until hematologic or renal recovery. No dose reduction unless criteria below are met
ANC <500/mm^3 in preceding cycle	Permanently reduce topotecan dose to 0.75 mg/m^2 or administer prophylactic G-CSF during subsequent cycles
Platelets <25,000/mm^3 in preceding cycle	Permanently reduce topotecan dose to 0.75 mg/m^2
Creatinine clearance 20 mL/min to 39 mL/min in preceding cycle	Permanently reduce topotecan dose to 0.75 mg/m^2

Special safety considerations for topotecan:

- Topotecan-induced neutropenia can lead to neutropenic colitis, which can be fatal. In participants presenting with neutropenia, fever, and a compatible pattern of abdominal pain, consider the possibility of neutropenic colitis.
- For participants for whom the dose was increased to 1.25 mg/m^2 after the first cycle and then experienced any toxicity requiring dose reduction, the recommended first dose reduction is to 1.0 mg/m^2.
- Topotecan can cause interstitial lung disease (ILD), which can be fatal. Monitor participants for symptoms indicative of ILD (cough, fever, dyspnea, or hypoxia), and discontinue topotecan if a new diagnosis of ILD is confirmed.

10.7.2. Recommended Dose Modifications for Irinotecan

The starting dose for irinotecan is 100 mg/m^2 or 125 mg/m^2 weekly × 4, followed by 14 days off treatment. For participants who experience toxicity with 125 mg/m^2 (described in Section 6.1.2), the recommended first dose reduction is to 100 mg/m^2. Participants who experience toxicity at 100 mg/m^2 will undergo a first dose reduction to 75 mg/m^2. Participants who experience toxicity at 75 mg/m^2 will undergo a second dose reduction to dose level of 50 mg/m^2.

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea has fully resolved. Treatment should be delayed for 1 to 2 weeks to allow for recovery of irinotecan-related toxicities. If the participant has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

Worst Toxicity, NCI Grade[b]	**During a Cycle of Therapy[a]**	**At Start of Next Cycle of Therapy (after adequate recovery), Compared with the Starting Dose of the Previous Cycle[a]**
Neutropenia		
1 (1500 – 1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000 – 1499/mm^3)	↓ 25 mg/m^2	Maintain dose level
3 (500 – 999/mm^3)	Omit dose level until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2
4 (<500/mm^3)	Omit dose level until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic Fever	Omit dose level until resolved, then ↓ 50 mg/m^2	↓ 50 mg/m^2
Other Hematologic Toxicities	Dose modifications for leucopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as those recommended for neutropenia above	
Diarrhea		
1 (2 – 3 stools/day)[c]	Maintain dose level	Maintain dose level
2 (4 – 6 stools/day)[c]	↓ 25 mg/m^2	Maintain dose level
3 (7 – 9 stools/day)[c]	Omit dose level unit resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2
4 (≥10 stools/day)[c]	Omit dose level until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2
Other nonhematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	↓ 25 mg/m^2	Maintain dose level

3	Omit dose level until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2
4	Omit dose level until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2

a. All dose modifications should be made based on the worst preceding toxicity.
b. NCI- CTCAE (version 5.0).
c. All numbers refer to increase over number of pre-treatment number of stools/day.
d. Excludes anorexia, alopecia, fatigue, asthenia, and laboratory abnormalities that are not considered to be clinically significant.

Source: CAMPTOSAR prescribing information, Pfizer, January 2020

10.7.3. Recommended Dose Modifications for Gemcitabine

The dose reduction guidelines for gemcitabine for myelosuppression on the day of treatment are presented below.

Treatment Day	Absolute Neutrophil Count (× 106/L)		Platelet Count (× 106/L)	% of Full Dose
Day 1	≥1500	And	≥100,000	100%
	<1500	Or	<100,000	Hold
Day 8	≥1500	And	≥100,000	100%
	1000 to 1499	Or	75,000 to 99,999	50%
	<1000	Or	<75,000	Hold

The dose reduction guidelines for gemcitabine for myelosuppression in the preceding cycle are presented below.

Occurrence	Myelosuppression During Treatment Cycle	Dose Modification
Initial occurrence	ANC <500 × 106/L for more than 5 days ANC <100 × 106/L for more than 3 days Febrile neutropenia Platelets <25000 × 106/L Cycle delay >1 week due to toxicity	Permanently reduce gemcitabine to 800 mg/m^2 on Days 1 and 8
Subsequent occurrence	If any of the above toxicities occurred after the initial dose reduction	Permanently reduce gemcitabine to 800 mg/m^2 on Day 1 only

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Withhold gemcitabine or reduce the dose by 50% for other severe (grade 3 or 4) nonhematologic toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

Source: GEMZAR prescribing information, Eli Lilly and Company, May 2019

10.7.4. Recommended Dose Modifications for Vinorelbine

Hematologic Toxicity

Neutrophils on Day of Treatment (cells/mm^3)	Percentage of Starting Dose of Vinorelbine
≥1500	100%
1000 to 1499	50%
<1000	Do not administer vinorelbine. Repeat neutrophil count in 1 week. If 3 consecutive weekly doses are held because neutrophil count is <1000/mm^3, discontinue vinorelbine
NOTE: For participants who experience fever and/or sepsis while neutrophil count is <1500 or participants who had 2 consecutive weekly doses held due to neutropenia, subsequent doses of vinorelbine should be:	
≥1500	75%
1000 to 1499	37.5%
<1000	Do not administer vinorelbine. Repeat neutrophil count in 1 week.

Hepatic Impairment/Toxicity

Serum Total Bilirubin Concentration (mg/mL)	Percentage of Starting Dose of Vinorelbine
≤2.0	100%
2.1 to 3.0	50%
>3.0	25%

Source: NAVELBINE prescribing information, GlaxoSmithKline, 2002

Concurrent hematologic toxicity with hepatic impairment

In participants with both hematologic toxicity and hepatic impairment, administer the lower of the doses based on the corresponding starting dose of vinorelbine determined from the respective schemas above.

Neurologic toxicity

Discontinue vinorelbine for NCI-CTCAE grade 2 or higher peripheral neuropathy or autonomic neuropathy causing constipation.

10.7.5. Recommended Dose Modifications for Single Agent Pemetrexed

Hematological Toxicities	**Pemetrexed dose (mg/m^2)**
Nadir ANC < 500/mm^3 and nadir platelets ≥ 50,000/mm^3	75% of previous dose
Nadir platelets < 50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose
Nadir platelets < 50,000/mm^3 with bleeding[a], regardless of nadir ANC	50% of previous dose
Non-hematological Toxicities	**Pemetrexed dose (mg/m^2)**
Any grade 3 or 4 toxicities except mucositis	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of grade) or grade 3 or 4 diarrhea	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose

a. These criteria meet the CTC version 2.0 (NCI 1998) definition of ≥ CTC grade 2 bleeding.
Source: ALIMTA prescribing information, Eli Lilly and Company, Sep 2008

10.8. APPENDIX 8: Investigator Signature Page

Investigator Statement and Signature

I have read the attached protocol entitled "A Randomized, Open-Label, Phase 3 Trial of Tisotumab Vedotin vs Investigator's Choice Chemotherapy in Second- or Third-Line Recurrent or Metastatic Cervical Cancer".

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

10.9. APPENDIX 9: Abbreviations

1L	first-line
2L	second-line
3L	third-line
ADA	anti-drug antibody
ADC	antibody-drug conjugate
aPTT	activated partial thromboplastin time
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest X-ray
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EQ-5D	standardized instrument developed as a measure of HRQOL
FA	final analysis
FDA	US Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GOG	Gynecologic Oncology Group
GSP	group sequential procedure
HBsAg	hepatitis B surface antigen

HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	hazard ratio
HRQOL	health-related quality of life
IA	interim analysis
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
IRC	independent review committee
IRR	infusion-related reaction
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
MDRD	Modification of Diet in Renal Disease
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NR	not reported
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
Q3W	every 3 weeks
QLQ-C30	Quality of Life of Cancer Patients questionnaire
QLQ-CX24	Quality-of-Life questionnaire cervical cancer module

RECIST	Response Evaluation Criteria In Solid Tumors
r/mCC	recurrent/metastatic cervical cancer
RNA	ribonucleic acid
RTFM	randomization and trial supply management
SAE	serious adverse event
SoA	schedule of activities
SUSAR	serious unexpected suspected adverse reactions
TEAE	treatment-emergent adverse event
TF	tissue factor
TTR	time-to-response
TV	tisotumab vedotin
ULN	upper limit of normal
VAS	visual analog scale

"Study treatment" is used to refer to either tisotumab vedotin or any of the chemotherapy options.

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