30 January 2025
EMA/59170/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tivdak

International non-proprietary name: tisotumab vedotin

Procedure No. EMEA/H/C/005363/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1L	first line
2L	second line
3L	third line
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate transaminase
AUC	area under the concentration-time curve
BICR	blinded independent central review
BLA	biologics license application
BOR	best overall response
C_{max}	maximum serum concentration
CC	cervical cancer
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	linear clearance
C_{max}	maximum serum concentration
CMC	chemistry, manufacturing, and controls
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
ESMO	European Society of Medical Oncology
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOP1	end of phase 1
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration

FIGO	International Federation of Gynecology and Obstetrics
FIH	first-in-human
GHS	global health status
GOG	Gynecologic Oncology Group
HPV	human papillomavirus
HR	hazard ratio
IND	Investigational New Drug Application
iPSP	initial paediatric study plan
IRC	Independent Review Committee
ISS	integrated summary of safety
ITT	intention to treat
IV	intravenous
KN-826	KEYNOTE826
mCC	metastatic cervical cancer
MedDRA	medical dictionary for regulatory activities
MMAE	monomethyl auristatin E
NA	not applicable
NCCN	National Comprehensive Cancer Network
NRG	Name Review Group
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-(L)1	programmed cell death ligand 1
PIP	paediatric investigation plan
PFS	progression-free survival
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
popPK	population pharmacokinetic
PR	partial response
PT	preferred term
Q3W	every 3 weeks
QOL	quality of life
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia
RDI	relative dose intensity
RECIST	response evaluation criteria in solid tumors
RMP	risk management plan
RP2D	recommended phase 2 dose
r/mCC	recurrent or metastatic cervical cancer
SD	stable disease
SAE	serious adverse event

sBLA	supplemental biologics license application
SCAR	severe cutaneous adverse reaction
SCS	summary of clinical safety
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
SOC	standard of care
TAb	total antibody
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TF	tissue factor
TRAE	treatment-related adverse event
ULN	upper limit of normal
US	United States
vcMMAE	valine-citrulline monomethyl auristatin E

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 12 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Tivdak, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

The applicant applied for the following indication:

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0216/2019 on the granting of a product-specific waiver.

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4. Applicant's request for consideration

1.4.1. New active substance status

The applicant requested the active substance tisotumab vedotin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
29 May 2019	EMA/CHMP/SAWP/272225/2019	Kristian Wennmalm, Joao Manuel Lopes de Oliveira

The scientific advice pertained to the following non-clinical and clinical aspects:

- Adequacy of the non-clinical toxicology studies
- Whether the defined study population represents a population with an unmet medical need in the context of a conditional marketing authorisation (CMA) application; Design of the phase III trial GCT1015-07 including study population, control arm, primary endpoints, statistical analysis plan (sample size, assumptions and statistical analysis); Adequacy of the phase II study (GCT1015-04) to support a CMA application and of the phase III trial (GCT1015-07) to serve as a confirmatory trial should a CMA be granted.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: Peter Mol

The application was received by the EMA on	12 January 2024
The procedure started on	1 February 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	22 April 2024
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	29 April 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	6 May 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	30 May 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	15 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs oint assessment report on the responses to the list of questions to all CHMP and PRAC members on	24 September 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	17 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to	11 October 2024

all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tivdak on	30 January 2025
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	30 January 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Cervical cancer is the fourth most common cancer in women with 604 000 new cases and 342 000 deaths worldwide in 2020 (Sung 2021). In Europe, over 58,000 women were diagnosed with cervical cancer in 2020, out of which nearly 26,000 died from the disease (Ferlay 2020). Cervical cancer consists of two main histologic subtypes, squamous cell carcinoma (~75%) and adenocarcinoma (~25%) (Adegoke 2012), with other histologic subtypes being rare (e.g. small cell carcinomas, rhabdomyosarcoma). Cervical cancer is associated with human papillomavirus (HPV) infection in nearly all cases (Walboomers 1999), with subtypes HPV 16 and 18 found in over 70% of cervical cancers (Li 2011). Screening with the Papanicolaou (Pap) test since the 1950s, with subsequent incorporation of HPV DNA testing, has been associated with decreased cervical cancer mortality in the US and other developed countries (Wang, 2004). Although vaccination against high risk strains of HPV is projected to gradually decrease the global incidence of cervical cancer in the coming decades, the burden of this disease remains profound (Simms, 2019). Effective immunisation against HPV and screening for cervical dysplasia can help prevent cervical cancer.

2.1.3. Clinical presentation and diagnosis

Early cervical cancer is usually asymptomatic; the most common symptoms at presentation for later stages are dysmenorrhea and postcoital bleeding. Approximately 43 percent of patients have localised disease at diagnosis, 35 percent have regional disease, and 15 percent have distant metastases (Siegel 2024). Despite high cure rate of the primary treatment of cervical cancer, the risk of recurrence is substantial and correlated to initial disease stage. For women who underwent curative-intent therapy for cervical cancer, the predominant site of disease recurrence is local (ie, at the vaginal apex) or regional (ie, pelvic sidewall). Distant metastases or multiple recurrence sites can develop in 15 to 61 percent of patients, usually within the first two years of completing treatment. Patients with suspicious findings on physical examination should undergo biopsy and additional radiologic examination should be performed to estimate the extent of the disease.

According to the Surveillance, Epidemiology, and End Results (SEER) database, in the US about 15% of cervical cancer patients are diagnosed with metastatic disease and the 5-year overall survival (OS) for patients with metastatic disease is approximately 19% (National Cancer Institute 2023).

2.1.4. Management

Patients with locoregional recurrence should be offered surgery or radiotherapy, if the disease is amenable for it.

In case of primary metastatic cervical cancer or recurrence ineligible for local treatments, patients should be offered systemic therapy.

Current recommended regimens (ESMO and NCCN guidelines) for the **first line therapy** are presented in the table below.

Table 1 Current recommended regimens (ESMO and NCCN guidelines)

Regimen	Key results of studies
Platinum-based chemotherapy plus bevacizumab OR Platinum-based chemotherapy for bevacizumab ineligible patients	GOG-240 Study: Addition of bevacizumab resulted in increase of Median OS 17 months vs. 13.3 months (HR 0.71), PFS 8.2 months vs. 5.9 months and ORR 48% vs. 36% compared to chemotherapy alone.
For tumours with PDL-1 CPS≥1: Pembrolizumab plus platinum-based chemotherapy with/ without bevacizumab	KN-826 Study: Addition of Pembrolizumab resulted in increase of Median OS 28.6 months vs. 16.5 months (HR 0.60), PFS 10.5 months vs. 8.2 months and ORR 69% vs. 51% compared to placebo/chemotherapy +/- bevacizumab.

Second-line treatment

Treatment options for patients who have progressed on the first line treatment are limited. Patients who were not previously exposed to checkpoint inhibitors can be offered cemiplimab (EMEA/H/C/004844-II-0026 issued on18/11/2022 based on the EMPOWER-Cervical 01 study (also known as Study 1676). Cemiplimab improved OS relative to single-agent chemotherapy (12.0 versus 8.5 months; HR 0.69, 95% CI 0.56-0.84), as well as objective response rates (16 versus 6 percent). This trial did not allow recruitment of subjects previously treated with anti-PD-1 agents. Thus, there are no data to support use of cemiplimab in 2L+ after previous anti PD-1 therapy in 1L.

Other options are single drug regimens, which have low response rates and poor outcomes (see table below; source ESMO guidelines 2020, Marth et al).

Table 2 Second line therapy for metastatic cervical cancer

SECOND-LINE THERAPY FOR METASTATIC CERVICAL CANCER

AGENT	N	CR + PR, %	PFS, MONTHS	OS, MONTHS
Bevacizumab	46	11	3.4	7.3
Topotecan	94	13-19	2.1-2.4	6.4-6.6
Vinorelbine	44	14	–	–
Gemcitabine	22	5	2.1	6.5
Albumin-bound paclitaxel	35	29	5.0	9.4
Docetaxel	23	9	3.8	7.0
Pemetrexed	72	14-15	2.5-3.1	7.4-8.8
Irinotecan	42	21	4.5	6.4
Sunitinib	19	0	3.5	–
Erlotinib	28	0	1.9	5.0
Lapatinib	78	5	4.2	9.7
Pazopanib	74	9	4.5	12.7
Pegylated liposomal doxorubicin	27	11	3.2	8.9

CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response

Unmet medical need:

Overall, the shift in treatment landscape with pembrolizumab becoming the standard of care (SOC) in 1L in combination with chemotherapy with or without bevacizumab leaves limited treatment options in the 2L and beyond setting.

2.2. About the product

Tisotumab vedotin (Tivdak) is an antibody-drug conjugate (ADC) composed of a human tissue factor (TF)-specific monoclonal immunoglobulin G1κ (IgG1κ) antibody (tisotumab; HuMax-TF) chemically conjugated via a protease-cleavable valine-citrulline (vc) linker to the microtubuledisrupting agent monomethyl auristatin E (MMAE), a dolastatin 10 analog.

TF is a transmembrane glycoprotein, which is aberrantly expressed in tumour cells and associated stromal cells in a broad range of solid cancers. Experimental studies suggest that tumour cells benefit from both TF pro-coagulant activity and TF-induced intracellular signaling (Versteeg 2015). Expression of TF in tumours has been associated with poor prognosis and an enhanced frequency of tumour metastasis (Nitori 2005; Regina 2009).

Tisotumab vedotin acts by binding to TF-positive cells. Once bound, the tisotumab vedotin: TF complex is internalised and trafficked to the lysosomes where the vc linker is cleaved, subsequently releasing MMAE. Tisotumab vedotin has multiple mechanisms for tumour cell killing, including MMAE-mediated direct and bystander cytotoxicity, ICD, ADCC, ADCP, and inhibition of TF: activated factor VII (FVIIa)-dependent downstream signaling.

The approved indication is:

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

Treatment with Tivdak should be initiated and supervised by a physician experienced in the use of anticancer therapies. Prior to the first infusion and as clinically indicated, an eye care professional should conduct an ophthalmic exam, including visual acuity and slit lamp exam.

The recommended dose of Tivdak is 2 mg/kg (up to a maximum of 200 mg for patients ≥ 100 kg) every 3 weeks until disease progression or unacceptable toxicity.

The recommended Tivdak dose reduction schedule is provided in Table 1. Tivdak should be permanently discontinued in patients who cannot tolerate 0.9 mg/kg.

Table 3: Dose reduction schedule

	Dose level
Starting dose	2 mg/kg (up to maximum of 200 mg)
First dose reduction	1.3 mg/kg (up to maximum of 130 mg)
Second dose reduction	0.9 mg/kg (up to maximum of 90 mg)

The recommended dose modifications for adverse reactions are provided in Table 2. Patients should be referred to an eye care professional as soon as possible for an assessment of new or worsening ocular symptoms.

Table 4: Dose modifications

Adverse reaction	**Severity***	**Occurrence**	**Dose modification**
Keratitis	Grade 1	Any	Withhold dose until clinically stable, then resume treatment at the same dose.
	Grade 2	First occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level.
		Second occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level. If no resolution to Grade ≤ 1, permanently discontinue.
		Third occurrence	Permanently discontinue.
	Grade 3 or 4	Any	Permanently discontinue.
Conjunctival ulceration	Grade 1 or 2	First occurrence	Withhold dose until clinically stable, then resume treatment at the next lower dose level.
		Second occurrence or more	Withhold dose until clinically stable, then resume treatment at the next lower dose level. If no stabilisation or improvement, permanently discontinue.
	Grade 3 or 4	Any	Permanently discontinue.
Conjunctival or corneal scarring or symblepharon	Any grade	Any	Permanently discontinue.
Conjunctivitis and other ocular reactions	Grade 1	Any	Withhold dose until clinically stable, then resume treatment at the same dose.
	Grade 2	First occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the same dose.
		Second occurrence	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level. If no resolution to Grade ≤ 1, permanently discontinue.
		Third occurrence	Permanently discontinue.
	Grade 3 or 4	Any	Permanently discontinue.
Peripheral neuropathy	Grade 2 or 3	Any (initial or worsening of pre-existing condition)	Withhold dose until Grade ≤ 1, then resume treatment at the next lower dose level.
	Grade 4	Any	Permanently discontinue.

Adverse reaction	Severity*	Occurrence	Dose modification
Severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS))	Suspected (any grade)	Any	Immediately withhold dose and consult a specialist to confirm the diagnosis.
	Confirmed Grade 3 or 4	Any	Permanently discontinue.

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening

2.3. Type of application and aspects on development

The clinical development program of tisotumab vedotin included multiple open-label studies (phase 1/2 and 2) across different tumour types. The RP2D dose of 2.0 mg/kg was selected in the GEN701 study and this dose was further evaluated in 4 studies, including the pivotal study for this application. Two further studies in Japanese subjects are ongoing. The overall clinical development plan is endorsed.

2.1. General comments on compliance with GMP, GLP, GCP

GCP

The applicant stated that the study was conducted in accordance with applicable regulations/guidelines set in the European Union (EU) Directive 2001/20/EC and 2005/28/EC; and with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

The applicant provided information on GCP serious breaches reported to the health authorities (1 in UK, 2 in Spain and 1 in Hungary). All were related to personal information being released by site staff to a study vendor. In all instances, the personal information was contained via the vendor's process. Corrective and preventative actions were implemented to mitigate the incidents.

Table 5 List of GCP inspections, as indicated by the applicant

Site (full address)	Country	Date of inspection	Regulatory Agency
Seagen 21823 30th Drive Southeast Bothell, WA 98021	USA	6-9 June 2023	MHRA
National University Hospital 1E Kent Ridge Road Singapore 119228	Singapore	10-12 October 2023	Singapore HSA
Hospital Universitario 12 de Octubre Avenida de Cordoba, s/n Madrid, Spain 28041	Spain	12, 14-16 February 2024	FDA
National Cancer Center Hospital 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045 Japan	Japan	4-8 March 2024	FDA

Source: ema-cover-appendix-4

Based on the review of clinical data, the CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

GLP

The non-clinical program of tisotumab vedotin comprised of GLP-compliant pivotal toxicology studies including repeat-dose toxicity, toxicokinetics, genotoxicity, developmental and reproductive toxicity and tissue cross-reactivity. Good Laboratory Practice-compliant safety pharmacology evaluations of the central nervous, pulmonary and cardiovascular systems were also completed.

The pivotal toxicity studies as well as safety pharmacology investigations were conducted under an extensive GLP audit program and in general appeared to be GLP compliant.

2.2. Quality aspects

2.2.1. Introduction

Tisotumab vedotin (HuMax-TF-ADC) is an antibody-drug conjugate (ADC) composed of a human tissue factor (TF)-specific monoclonal immunoglobulin G1κ (IgG1κ) antibody (tisotumab) chemically conjugated via a protease-cleavable valine-citrulline (vc) linker to the microtubule-disrupting agent monomethyl auristatin E (MMAE), a dolastatin 10 analog. Separate active substance sections are provided below for the antibody intermediate, the vcMMAE intermediate and the tisotumab vedotin active substance.

The finished product is presented as a powder for concentrate for solution for infusion containing 40 mg of tisotumab vedotin as active substance.

Other ingredients are: L-histidine, L-histidine hydrochloride monohydrate, sucrose and D-mannitol.

The product is available in a 10mL Type I glass vial with gray butyl rubber stopper, plug and top, 20 mm seal with silver colored aluminum cap and garnet disc. Each carton contains 1 vial.

2.2.2. Active substance (antibody intermediate)

General information (antibody intermediate)

Tisotumab is a human IgG1κ antibody composed of two kappa light chains and two IgG1 heavy chains covalently associated by disulfide bridges. There is a single N-linked glycosylation site in each heavy chain.

Manufacture, process controls and characterisation (antibody intermediate)

Description of manufacturing process and process controls

The name, address and responsibility of each manufacturer involved in the tisotumab manufacturing process and testing has been provided. GMP certificates are presented.

A frozen working cell bank (WCB) vial is removed from liquid nitrogen storage and thawed. The cell culture is expanded in several steps before being transferred to the production bioreactor. Process parameters and in-process controls (IPCs) for vial thaw, subculture and expansion steps, and in production bioreactor are provided. The unprocessed bulk is clarified, followed by 0.2 µm filtration.

Purification includes virus inactivation, capture of tisotumab from the harvest fluid by a Protein A chromatography column, followed by chromatography steps for impurity removal, viral filtration, and diafiltration into the formulation buffer. Tisotumab is frozen before being transported and stored.

Reprocessing and refiltration for certain process steps were proposed and accepted.

Control of materials

Raw materials are purchased from approved suppliers and tested according to material specifications. The specifications for compendial materials are based on the relevant monographs. The water for injections (WFI) used throughout manufacturing for media and buffer preparations meets USP and Ph. Eur. standards. Other than the mammalian cell line expressing the product, no materials of animal origin or antibiotics are used in the tisotumab manufacturing process. Raw materials for cell culture and purification and their control are adequately described. Specifications of non-compendial raw materials are presented.

The anti-tissue factor (TF) antibody, tisotumab, is a human IgG1κ antibody produced in Chinese hamster ovary (CHO) cells. The sequences of the variable region of the light chain and the heavy chain, respectively, were obtained from a human anti-TF monoclonal antibody generated by hybridoma technology using a human IgG1κ transgenic mouse strain.

A two-tiered cell bank system is established. The master cell bank (MCB) vials are stored in the vapour phase of liquid nitrogen (≤ -130° C) held at two sites with controlled access. No raw materials of animal or human origin were used to generate the MCB. The tisotumab MCB has been shown to be free from microbial organisms and mycoplasma. The tisotumab WCB, was generated in accordance with cGMP requirements. The WCB was tested and characterised according to ICH Q5B, Q5D, and Q5A(R1). Virus testing was performed. The generation of an end of production cell bank at the limit of *in vitro* cell age (LIVCA) is adequately described. Description and characterisation of integration of light chain (LC) and heavy chain (HC) cDNA sequences into the host cell genome is sufficiently described. It is concluded that the WCB is suitable for manufacture of tisotumab.

Cell bank stability is discussed. A protocol for the establishment of future WCB is provided and is considered acceptable.

Control of critical steps and intermediates

Process characterisation studies have identified steps in the tisotumab manufacturing process with CPPs. There are no process intermediates isolated and stored during the tisotumab manufacturing process.

Process validation

Batch uniformity was demonstrated and all results from different sample points met the acceptance criteria. In-Process Product Pool hold times and conditions were validated based on chemical stability and bioburden/endotoxin assessment.

For PPQ, pre-defined acceptance criteria were established for parameters to demonstrate acceptable process performance, batch-to-batch consistency, and appropriate microbial control for commercial manufacturing. Where an excursion to an acceptable range was recorded, an investigation was recorded in the manufacturer's quality system and the impact to the product was assessed.

All performance indicators and quality attributes monitored for PPQ met the acceptance criteria and demonstrated process consistency and robustness of the manufacturing process.

Reprocessing is allowed in the event of a post-use integrity test failure or a breach of system integrity of the virus reduction filter (VRF) or the bulk fill terminal 0.2 µm filter. It is confirmed that reprocessing cannot be performed as a result of a bioburden excursion. Concurrent validation is proposed and will be initiated at the first instance of refiltration. This is acceptable but according to EMA/CHMP/BWP/187338/2014 guidelines requirements, the applicant has committed to providing validation of reprocessing data, as soon as they are available. **(REC)**

The performance of Protein A resin and AEX/HIC membranes was assessed in small scale studies to define the lifetime of the materials. It is declared that commercial scale validation studies will continue concurrent with commercial manufacturing to confirm the protein A column lifetime. The results of the completed resin lifetime studies will be submitted when available. **(REC)**

Initial manufacturing process hold times, with regard to chemical stability, were established at small scale during development of the tisotumab process. Process hold times for commercial manufacture of tisotumab were defined from the chemical stability, the microbial stability, and a supplemental microbial hold time study.

An evaluation of the transportation requirements for tisotumab was performed to identify validation activities required to ensure that the shipping system maintains product integrity while consistently maintaining the appropriate temperature range during transit. Tisotumab is an aqueous formulation stored and shipped in a frozen format. The information provided in relation to the conducted shipping validation is considered satisfactory.

Manufacturing process development

During development, tisotumab has been manufactured by several manufacturing processes at different scales. The potential impact on product quality that may result in safety and efficacy changes from applied process changes were assessed by analytical comparability comparing the product quality pre- and post-changes. Analytical comparability was assessed by comparison of release data, extended physicochemical and biological characterisation data and stressed stability data. Based on results from the analytical comparability assessments, it is concluded that tisotumab materials manufactured from these processes are comparable.

As part of the process characterisation methodology, process risk assessment is conducted to identify the process parameters requiring further characterisation. Process parameter criticality and acceptable ranges for the parameters are determined based on process and product impact after process characterisation.

Determination of process parameter acceptable ranges is based on the process risk assessment, process parameters that potentially have impact on performance indicators and critical quality attributes were identified to be further evaluated through process characterisation studies. The outcome of the downstream process characterisation study results is reflected in the overall control strategy. Proposed parameter classifications for the individual steps as well as the defined acceptable ranges and acceptance criteria are considered adequate.

Characterisation

Tisotumab is an IgG1κ monoclonal antibody directed against tissue factor, composed of two kappa light chains and two IgG1 heavy chains. Tisotumab is produced in a CHO cell line, and manufactured using standard mammalian cell cultivation and purification technologies. Tisotumab is an antibody intermediate for further processing into tisotumab vedotin. A consensus N-glycosylation site is located at heavy chain Asn298 (numerical numbering) and is predominantly occupied with a core fucosylated biantennary glycan. Tisotumab vedotin active substance mechanisms of action (MoAs) include targeted delivery of vcMMAE via tissue factor (TF) binding and internalisation, and the additional Fc mediated effector functions antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). To assess which properties of the antibody intermediate should be controlled to ensure proper biological activity of tisotumab vedotin, comprehensive physicochemical and biological characterisation of tisotumab was performed.

The test methods are well described. Results are presented in tables, including comparison of theoretical vs experimental values, where applicable. The CDRs are sequenced and the target epitope is defined.

Biological activity was assessed.

Glycosylation and glycation analysis, size variants and charge variants were analysed. Glycans with known potential to significantly influence effector function activity were evaluated.

The purity, monomer vs dimer content and Fab/Fc was analysed. Effect of variants/impurities on biological activity of tisotumab was assessed. Charge variants were characterised for biological activity and showed no altered binding behaviour to the target.

Degradation was conducted under extreme stress conditions to characterise tisotumab degradation pathways and it was shown that the resulting degradation products were adequately monitored by the analytical methods used during release and stability testing of tisotumab, supporting the control strategy in place.

Process-related impurities include impurities from the Chinese Hamster Ovary (CHO) host cell used to manufacture tisotumab or from raw materials used during cell culture and purification process. Process-related impurities from the host cell line consist of CHO DNA and host cell proteins (HCP). It was demonstrated that process-related impurities were controlled during PPQ.

Product-related impurities have been identified and are controlled by validated test methods.

Specification (antibody intermediate)

Specifications are proposed as defined by ICH Q6B. The setting of specifications consists of the selection of suitable attributes and analytical procedures, and the setting of appropriate acceptance criteria. The release specification includes general tests, test for identity, purity and impurity tests, test for protein concentration, potency, as well as tests for safety.

Overall, the parameters included in the specification are found adequate to control the quality of the tisotumab intermediate.

Analytical procedures

Analytical methods are tabulated and adequately described in the referenced subsections. Stability-indicating methods are clearly marked. For the different methods the materials (including standards), sample preparation and assay procedures are clearly described. System suitability criteria are in place for all methods.

Compendial and non-compendial methods are used for release and stability testing of tisotumab. The compendial analytical procedures are performed in accordance with the methods described in the relevant pharmacopoeia current at the time of testing. Verification results summary for the compendial test methods are presented into dossier.

Non-compendial methods are described in sufficient detail. System suitability and reporting results are presented for all non-compendial methods. Overall, the documentation provided for the validation of analytical procedures for tisotumab is considered comprehensive. Summaries of the validation of the analytical procedures have been provided.

Validation parameters are clearly indicated with results for all methods. Working ranges were defined as applicable.

Reference materials

The primary reference standard was established. The working reference standard was established concurrently with the primary reference standard from the parent batch. Certification and characterisation of the primary reference standard is also applicable for establishment of the working reference standard as the two reference standards are identical with respect to the parent batch of tisotumab, date of manufacture, aliquot volume, storage container, and temperature conditions.

Batch analysis

Batch data from multiple batches has been provided. These batches include batches from processes during development. Registration/PPQ batches and additional commercial scale batches. All batches meet the specification at place at the time of testing. The provided batch data demonstrates adequate batch-to-batch consistency.

Container closure

The container closure system itself is sufficiently described and characterised and is deemed suitable for storage of the tisotumab antibody intermediate. Furthermore, the Extractable and Leachable Risk Assessment evaluating the potential risk of leachables and extractables during tisotumab manufacturing process and storage is provided.

Stability (antibody intermediate)

A shelf life of 60 months at ⩽-65°C is proposed for the antibody intermediate.

Tisotumab stability is monitored at the long-term storage temperature of ⩽ -65°C for up to 72 months. Stability studies have also been conducted at an accelerated storage condition of 5 ± 3°C and a stressed storage condition of 25 ± 2°C for selected batches.

When stored at the temperature of ≤65°C intended for long-term storage, all batches complied with the acceptance criteria at the time of testing as well as the proposed commercial specification. No changes were observed for any attribute evaluated up to 72 months of storage.

The stability data obtained at stressed temperature of 25 ± 2°C demonstrates that the attributes measured by icIEF, CE-SDS non-reduced, CE-SDS reduced and SE-HPLC are stability indicating. All tisotumab batches enrolled on stability displayed similar stability profiles for all attributes.

The shelf-life claim for tisotumab active substance intermediate of 60 months when stored at -65°C (intended storage temperature) is considered acceptable.

2.2.3. Active substance (drug-linker intermediate)

General information (drug-linker intermediate)

SGD-1006 (drug-linker intermediate), see **Figure 3**, is an intermediate in the manufacture of the antibody-drug conjugate. The payload MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis.

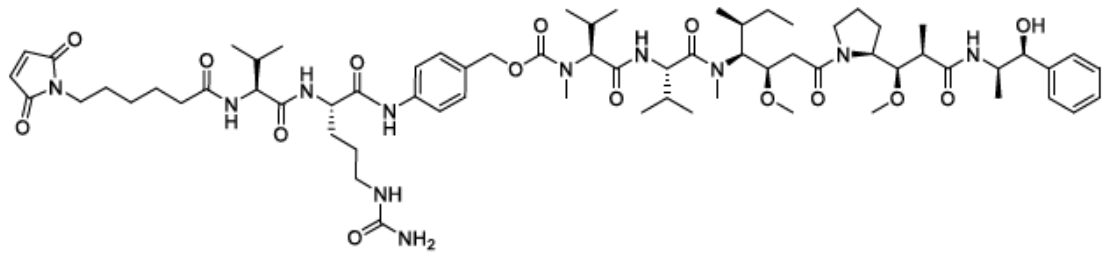


Figure 1: Structure of SGD-1006

Manufacture, process controls and characterisation (drug-linker intermediate)

Description of manufacturing process and process controls

Relevant documentation about the sites involved in the manufacture of SGD-1006 has been provided to show GMP compliance.

The SGD-1006 synthetic route is a solution phase, convergent synthesis which combines noncytotoxic (non-high potency) chemical precursor compounds to form the highly cytotoxic (high potency)

compounds SGD-1010 and SGD-1006 in a number of stages. The individual stages are described in detail, including the input materials and their amounts. IPCs are defined throughout the process.

The SGD-1006 manufacturing process is adequately described.

Control of materials

A list of materials and the stage of material use is provided. All raw materials, solvents, reagents, and auxiliary materials used in the manufacture of SGD-1006 are sourced from qualified vendors and are tested and released against pre-defined specifications. The SGD-1006 manufacturing process utilises six starting materials. The definition of these materials as staring material is mainly based on well-defined synthetic routes and their control. Specifications and adequate limits are defined for each of the staring materials including control of potential impurities.

Information on fate and origin of impurities, results from spiking and purging studies and process knowledge to support the specifications for related impurities are provided. The structure and control of specified impurities are also provided.

The lists of materials/reagents used for synthesis in separate stages are provided. In general, the quality of materials could be considered adequate.

Control of critical steps and intermediates

Critical process parameters together with their proven acceptable ranges were defined for parameters that have a demonstrated impact on SGD-1006 critical quality attributes. The IPCs are suitable to control the manufacturing process.There are no critical in-process controls in the SGD-1006 manufacturing process. Specifications with adequate limits are defined for intermediates which originate during processing.

Process validation

SGD-1006 process validation was performed. Original Process Validation documents for the manufacture of SGD-1006 are provided.

Some post-validation modifications were introduced and justified.

Manufacturing process development

Data demonstrate that the process transfer and scale-up during process development were successful. Overviews of process characterisation study results conducted are provided indicating target values, normal operating ranges (NORs) and proven acceptable ranges (PARs). In particular the amount of critical input materials was investigated in these studies. The PARs are reflected in the process description.

Characterisation

SGD-1006 has been characterised utilising several analytical techniques.

Impurities studies were conducted to understand the factors that are responsible for their formation, and the ability of the process to purge the impurities or their fate products. Impurities are controlled by IPCs or by implementation of specifications. A brief risk assessment is provided regarding genotoxic impurities including nitrosamines.

Specification (drug-linker intermediate)

The SGD-1006 specification provides assurance that the drug-linker intermediate is of suitable quality for use in the preparation of antibody-drug conjugate active substances. The SGD-1006 tests and acceptance criteria are based on manufacturing process knowledge and batch experience, and ICH Q3A, Q3C, Q3D guidelines.

Analytical procedures

Analytical procedures comprise methods in accordance with USP and Ph. Eur. and are employed to assess Appearance, identity, specific rotation, water content and identity, purity and assay (HPLC). Analytical methods for SGD-1006 batch release and stability testing are compendial and non-compendial, and their description is considered sufficient.

For tests that comply with Ph. Eur. or USP, a brief description is provided, which is acceptable.

For the non-compendial methods a more detailed description is provided. In general, the information provided is adequate. Validation results for each method are provided in accordance with ICH Q2(R1).

Reference Materials

Qualification results of the reference standards are provided. Purity factor was assigned. The requalification procedure provided is considered adequate.

Batch analysis

Batch analysis results from multiple batches confirm batch-to-batch consistency resulting in a stable SGD-1006 intermediate.

Container closure

The primary packaging configuration is USP Type III soda-lime amber glass jars closed with a polytetrafluoroethylene (PTFE, on product contact side) lined polypropylene screw cap or USP Type I amber glass bottle, closed with a screw cap made of fluorothermoplastic with a press-fit polytetrafluoroethylene coated silicone seal. The container closure system is sufficiently described and acceptable.

Stability (drug-linker intermediate)

A retest date of 36 months is proposed for the SGD-1006 Intermediate when stored at the recommended storage condition of -25 to -15 .The stability data demonstrate that SGD-1006 is stable and remains within acceptance criteria, with no degradation trends observed when stored at the recommended storage condition of –20 ±5 °C and the accelerated storage condition of 5 ± 3 °C.

Based on real-time long-term stability data from multiple lots of SGD-1006, the recommended re-test period of 36 months at -25 to -15 °C is considered acceptable.

2.2.4. Active Substance

General Information

Tisotumab vedotin is a tissue factor-specific (TF) antibody-drug conjugate consisting of a) the human IgG1κ anti-TF antibody, tisotumab, b) the microtubule-disrupting agent monomethyl auristatin E (MMAE), and c) a protease-cleavable valine-citrulline (vc) linker that covalently attaches MMAE to tisotumab (see

Figure 2). Tisotumab vedotin active substance is a heterogeneous mixture of related species with posttranslational modifications originating from the antibody intermediate, derivatised with vcMMAE, with the most abundant form of tisotumab vedotin having 4 drug molecules attached.

TF is a transmembrane glycoprotein, which is aberrantly expressed in tumour cells and associated stromal cells in a broad range of solid cancers. The anticancer activity of tisotumab vedotin results from the binding of the ADC to tissue factor-expressing tumour cells, followed by internalisation of tisotumab vedotin and subsequent release of MMAE via proteolytic cleavage of the valine-citrulline

linker. Intracellular MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis of the cells. The ADC can also induce ADCC and ADCP activity.

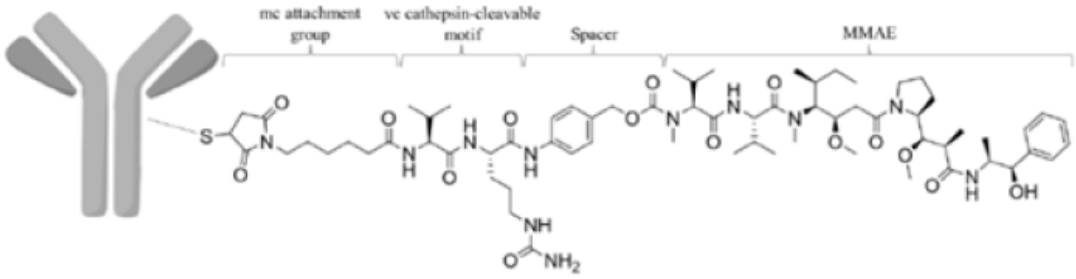


Figure 2: Tisotumab vedotin structure

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The batch scale is defined by the amount of tisotumab that goes into each batch of tisotumab vedotin active substance.

Tisotumab vedotin active substance is manufactured and tested at Lonza AG Visp, Switzerland. The name, address and responsibility of each manufacturer involved in the tisotumab vedotin (conjugation) manufacturing process and testing has been provided. GMP compliance has been adequately demonstrated.

The conjugation process is initiated by thawing and pooling of tisotumab, followed by partial reduction of the disulfide bridges of tisotumab using tris(2-carboxyethyl) phosphine hydrochloride (TCEP-HCl) as the reducing agent. The generated free thiol groups are then conjugated via the maleimide entity of the drug-linker vcMMAE. The manufacturing process consists of three main chemical steps – reduction, conjugation, and quench – followed by ultrafiltration/diafiltration (UF/DF) and the final formulation.

The steps of the process flow with identification of CPPs is given. IPCs are indicated for each process step, if applicable. No reprocessing is performed during production of tisotumab vedotin active substance.

Control of materials

Tisotumab vedotin active substance is made from tisotumab a monoclonal antibody (mAb) and a drug linker (DL) vcMMAE (also referred to as SGD1006). For the manufacturing process, the materials used are listed, their use in the respective process steps is indicated and specifications are listed for compendial and non-compendial materials. No novel excipients or components are used in the manufacturing of tisotumab vedotin active substance.

Compendial materials are received against pre-defined specifications established by the applicable compendial monograph. The process step where each raw material is used is indicated. All compendial raw materials are tested for identity at the manufacturing site as part of the incoming control testing.

Non-compendial materials are received against pre-defined specifications. Their specifications are provided.

A list of filters and membranes used in the active substance manufacturing process is provided. The specifications for filters and membranes by the drug substance manufacturers are provided.

Control of critical steps and intermediates

Critical steps together with acceptance criteria are identified. They are supported by pharmaceutical development, based on the manufacturer's experience and could be considered in general acceptable.

There are no process intermediates isolated during the tisotumab vedotin active substance manufacturing process. Two intermediates are used in the active substance manufacturing: tisotumab monoclonal antibody intermediate (mAb intermediate) and vcMMAE drug-linker intermediate (SGD-1006). These intermediates are controlled to ensure the quality of the active substance (refer to sections above).

Determination of CQAs and the overall integrated control strategy are described.

The IPCs are suitable to control the manufacturing process

Overall, the tisotumab vedotin active substance manufacturing process is considered adequately controlled.

Process validation

The tisotumab vedotin manufacturing process validation included three batches For all individual steps the pre-defined acceptance criteria were met and thus, the active substance manufacturing process is considered sufficiently robust and validated. Batch analysis data revealed that all three PPQ batches met the release specification limits.

Tisotumab vedotin batch uniformity was evaluated using PPQ batches. All results met the acceptance criteria, which are consistent with the tisotumab vedotin specification.

The UF/DF step was evaluated for clearance of process-related impurities such as excess free drug-related impurities (FDRI), DMA, and EDTA. The results of process-related impurities obtained from the three consecutive batches indicate that the process is capable if of efficient impurity clearance. Throughout the stage samples are taken.

A shipping validation summary is provided. Temperature excursions might be acceptable based stability data. Although the potential excursion is considered acceptable, such an event would be handled as deviation and trigger an investigation.

The applicant demonstrated that the manufacturing process is stable and ensures reproducible manufacture of active substance compliant to the specification.

In general, it has been demonstrated that each step of the manufacturing process is well controlled.

Manufacturing process development

During the course of development, tisotumab vedotin has been manufactured at two scales. With the scale-up and change of suite, changes in equipment for various manufacturing steps have been implemented. Furthermore, a few minor adjustments to the manufacturing process have been introduced. Analytical comparability comparing the product quality from the two scales was assessed. It is agreed that the impact of the scale changes on product quality can be expected to be marginal and the number of batches is accepted as the data indicate the small scale and large-scale derived material are comparable.

Potential CPPs have been identified based on prior knowledge evaluation, Cause and effect analysis and FMEA Parameters exceeding risk priority number (RPN) scores. Process parameters chosen for process characterisation include chemical steps and the UF/DF step. The classification as well as the defined acceptable ranges for CPPs and also the non-CPPs are consider justified based on DoE and OFAT results.

In summary, the applicant properly addressed the history of development of manufacturing process and discussed the impact on comparability. All changes made during process development are justified with respect to the impact on quality. The in-process data, combined with the batch data indicate that the process is capable of operating within defined parameters to generate product of the required product quality.

Characterisation

Physicochemical and biological characterisation was performed to determine the molar mass, primary and secondary structure, thermal stability, functional and immunological properties, potency, biological activity, glycoform structure, drug-load variants, size heterogeneity, and charge variants. All product-specific methods were validated, for most of the molecular features at least two orthogonal methods were employed. The test result section is very well structured, graphical displays and tabulated numerical data are provided. Biological activity of the active substance is compared against the tisotumab antibody. Impact of N-glycans and other PTMs on biological activity is assessed.

Potential degradation pathways of tisotumab vedotin were assessed under forced degradation conditions. Degradation was conducted under extreme stress conditions to characterise tisotumab vedotin degradation pathways and it was shown that the resulting degradation products were adequately monitored by the analytical methods used during release and stability testing of tisotumab vedotin supporting the control strategy in place.

Impurity clearance studies demonstrated that UF/DF effectively and robustly achieves appropriate clearance of tisotumab vedotin active substance process-related impurities. The drug-linker (vcMMAE) used in the manufacture of tisotumab vedotin active substance is added at the conjugation step. Product-related impurities are measured and controlled by release testing.

Overall, the structural and physicochemical characterisation of tisotumab vedotin active substance is considered comprehensive and sufficient.

The characterisation studies include release testing using the proposed commercial release analytical methods and extended characterisation methods to assess the primary, secondary and higher order structure, as well as post-translational modifications. Physicochemical characteristics have also been sufficiently addressed. In addition, the biological characteristics have been sufficiently addressed.

Overall, tisotumab vedotin active substance characterisation is acceptable, the rationality of applied biological assay for testing potency of active substance is provided.

Impurities

The applicant separately discusses process-related and product-related impurities.

Process-related impurities are derived from the manufacturing process. The clearance of those impurities was demonstrated using samples taken during the manufacturing of the PPQ.

Product-related impurities are molecular forms that may not have properties comparable to those of the desired product with respect to efficacy and safety. They are identified and shown to be consistent in commercial batches.

Specification

The active substance specification includes general tests, identity tests, purity tests, tests for potency, test for protein content, and safety tests. Overall, the parameters included in the drug substance specification are found adequate to control the quality of the tisotumab vedotin at release and is in accordance with ICH Q6, Ph. Eur. and based on comprehensive batch and stability data. Defined limits are considered appropriate. The justification for attributes which are not included in the tisotumab vedotin active substance specification is provided. This is acceptable.

Analytical procedures

The analytical test methods have been developed and appropriately validated for the release and stability testing of tisotumab vedotin active substance. Both compendial and non-compendial methods are used.

Non-compendial analytical methods used for active substance batch release and stability studies include identity, purity, potency, assay. For the non-compendial methods a more detailed description is provided, and it includes the method principle, equipment, reagents, sample preparation, procedure, analysis (calculations). Additionally, the system suitability criteria and for some of them representative chromatogram/electropherogram are provided. In general, the information provided is adequate.

The tests for appearance, pH, and osmolality are stated to comply with Ph. Eur. or USP, and no separate descriptions are provided. The tests for bioburden and bacterial endotoxins are stated to comply with Ph. Eur. or USP or JP, and a brief description is provided, which is acceptable.

All analytical procedures used for active substance batch release and stability testing have been appropriately verified (compendial procedures) or validated (product specific procedures). Non-compendial method validation was performed for standard parameters (specificity, accuracy, repeatability, intermediate precision, linearity, range, robustness, prepared sample stability, quantification limits, etc.) as applicable for the method. Each method was tested for stability indicating ability. The analytical method validations comply with ICH Q2.

The applicant evaluates potency by several methods, including evaluation of antigen binding in an ELISA and evaluation of cytotoxicity in a cell-based assay.

The information provided shows the suitability of established procedures for determination of specification parameters.

Reference materials

The primary reference standard was certified against a reference standard and the primary reference standard (PRS) parent batch underwent extended characterisation. All test results fulfilled predefined acceptance criteria. The PRS is requalified on an annual basis. The working reference standard was established concurrent with the manufacture of the primary reference standard . Annual requalification of the working reference standard is performed for its continued usage in batch release and stability testing of tisotumab active substance and finished product.

Batch analysis

The batches were tested by the test methods applied at the time of release. All results are within specifications in effect at the time of release and provides confirmation that the active substance is manufactured consistently. All tisotumab vedotin active substance batches manufactured from PPQ to date are listed. All batches met the release specifications in effect at the time of release.

Container closure

The primary packaging for tisotumab vedotin is HDPE bottles with silicone-lined white PP closure. The description and drawing for the primary packaging are provided. A risk assessment and study on leachables was conducted. Overall, the risk for leachables was considered low for the active substance process. Nonetheless, a leachables study was performed on the final container closure system.

Specifications for plastic materials for the HDPE bottle, PP closure and the closure liner are provided.

The suitability of the container and closure materials for storage of the tisotumab vedotin is demonstrated by passing the USP Class VI testing requirements and is verified by certification of conformance from the supplier.

The active substance is stored below -65°C. Data from freezing/ storage/ thawing study demonstrating the active substance container closure integrity and resistance to microbial burden under storage conditions was provided.

Stability

A shelf life of 60 months at -65°C is claimed for the active substance. The stability program of tisotumab vedotin has been developed following the principles outlined in ICH Q5C and Q1A(R2).

Stability studies for tisotumab vedotin are conducted under at the long-term storage temperature of -65°C for up to 60 months (0, 12, 24, 36, 48, 60 months). Stability studies have also been conducted at stressed storage conditions: 5 ± 3°C and 40 ± 2°C / 75 ± 5% RH for selected batches. The selected quality attributes for stability study are adequate and the stability study design is suitable.

Tested batches include clinical batches, commercial scale batches, including the PPQ/registration batches.

All batches complied with the acceptance criteria at time of testing as well as the commercial specification and thereby demonstrate the overall stability of tisotumab vedotin active substance, kept at -65°C. No meaningful trends were determined at the real conditions for tested quality attributes, discussion and graphical illustrations are provided.

Stress stability studies, freeze-thaw studies, photostability studies according to the ICH Q1B "Photostability Testing of New Active Substances and Medicinal Products" are provided.

In conclusion, the stability studies are designed in accordance with ICH Q5C Stability testing of biotechnological/biological products. No significant trends were observed at the intended storage temperature of -65°C for any test of any batches included in the stability programme.

Based on provided stability data from multiple lots of tisotumab vedotin, the recommended shelf-life and storage conditions are considered acceptable.

2.2.5. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

Tisotumab vedotin finished product is a sterile, preservative-free lyophilised powder, supplied in a single-dose vial and intended for intravenous infusion. Prior to administration, the finished product is reconstituted with 4.0 mL of sterile water for injections. The reconstituted solution is subsequently diluted in either sterile 0.9% sodium chloride injection, sterile 5% (w/v) dextrose injection, or Lactated Ringer's injection in an intravenous infusion bag prior to administration.

The composition of the finished product together with all excipients, their quantities per vial, functions and references to quality standards (Ph. Eur., USP, JP) are given. All excipients (L-histidine, L-histidine monohydrochloride, sucrose, and D-mannitol) are compendial and are tested in accordance with current compendial procedures.

Pharmaceutical development

The finished product was developed to ensure long-term stability at refrigerated (5 ± 3 °C) conditions during storage. Formulation robustness studies were conducted. The results demonstrated that the formulation is robust for the intended use at the recommended storage condition

During development, the finished product manufacturing process has been scaled up. Each process scale-up was supported by a comparability assessment.

A comprehensive list of quality attributes was generated. Consideration was given to a wide range of quality attributes. Each quality attribute was evaluated using general scientific knowledge, literature, and product-specific data. The criticality classification of quality attributes for tisotumab vedotin finished product is acceptable. Some of the defined CQAs are not expected to be impacted by the finished product manufacturing process. Process characterisation studies revealed that the non-CPPs are sufficiently controlled. Manufacturing process parameters impacting aseptic processing, sterility assurance, and product specific critical product quality attributes are defined as CPPs which is acknowledged.

The container closure system was concluded to be suitable for tisotumab vedotin finished product.

The risk of leachables from the primary container closure system is low over the shelf life. The overall microbial control strategy is designed with respect to aseptic processing GMP requirements.

Finished product in-use stability and compatibility studies were performed to support the stability of the reconstituted tisotumab vedotin finished product and the dosing solutions, in order to ensure their compatibility with components used for dose preparation and administration.

Chemical and physical in-use stability for the reconstituted solution in the vial has been demonstrated to support the in-use shelf life claim of up to 24 hours at 2°C to 8°C or for up to 8 hours at 9°C to 25°C. This is reflected in the Product Information.It is shown that the dosing solutions are stable when used as instructed. The dosing solutions are compatible with commonly used IV bags and IV tubing sets. With regard to In-use stability tisotumab vedotin finished product can be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to achieve a final concentration of 0.2 mg/mL to 2.4 mg/mL. The prepared dosing solution should be used immediately. If not administered immediately, the dosing solution might be stored refrigerated at 2-8°C for up to 18, 24, and 12 hours if diluted in with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection respectively which is acceptable.

The choice and rationale for selection of the container closure system for the commercial product is provided and is considered sufficient. The choice of materials for primary packaging has been justified. The discussion on the integrity of the container and closure system has been provided.

The compatibility of the finished product with reconstitution diluents has been adequately addressed and demonstrated.

Manufacture of the product and process controls

QP release of tisotumab vedotin is performed by Seagen B.V.,Evert van de Beekstraat 1 – 104, 1118 CL Schiphol, Netherlands.

The tisotumab vedotin finished product manufacturing process represents a standard fill and finish process for lyophilised finished products and is comprised of thawing, pooling and mixing, sterile filtration, aseptic filling, lyophilisation, capping and visual inspection. The individual steps are sufficiently detailed described. The process parameters are sufficiently described including IPCs and CPPs and processing times which were verified by process characterisation studies.

Critical process parameters and in-process controls were identified, primarily to ensure microbial control during the aseptic process.

Aseptic procedures include sterilisation and depyrogenation procedures for manufacturing equipment. The aseptic process is validated by media fills.

Three consecutive commercial scale PPQ batches were produced in order to support the validation of the manufacturing process for tisotumab vedotin finished product. The processes were executed and controlled within the predefined control ranges for the three recent PPQ batches.

Shipping conditions are appropriately validated.

Product specification, analytical procedures, batch analysis

The finished product specifications are defined in accordance with ICH Q6B and acceptance criteria and limits are proposed. Parameters tested include identity, purity, potency, quantity, as well as general (appearance, pH, osmolality, particles, reconstitution time, residual moisture) and safety (sterility, endotoxins, container closure integrity) tests.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

The risk assessment for potential nitrosamine impurities concluded that there is low to no nitrosamine risk for tisotumab vedotin finished product and no further nitrosamine testing nor other risk mitigations are necessary.

Analytical methods

Finished product-specific analytical procedures employ non-compendial and compendial methods, the latter are clearly identified (compendial reference). Testing methods are sufficiently described and verified or validated.

Reference materials

The reference standard used for finished product testing is the same as for the active substance.

Batch analysis

All provided production-scale batch results comply with the specification at the time of batch release as well as proposed commercial specification.

Container closure system

The primary packaging components consist of a 10R Type I glass vial suitable for lyophilisation and the volume requirements for finished product filling and reconstitution. The closure is a lyophilisation stopper with coating. The closed vials are sealed with an aluminum/plastic flip-off. With regard to leachables/extractables an assessment was conducted concluding that there is minimal risk of contact with the stopper during shelf life since tisotumab vedotin finished product is lyophilised and there is no solvent in the finished product to facilitate leachables.

Diagrams and specifications for the vial, stopper and seal are provided. Moreover, references to the relevant monographs of the Ph. Eur. together with the certificates of analysis of the components of the Container Closure System are provided.

Stability of the product

The claimed shelf life for tisotumab vedotin finished product at the intended storage temperature of 2-8°C is 60 months.

The stability studies are carried out in accordance with current guidelines. Stability studies are performed at the long-term storage condition (5°C ± 3°C), accelerated storage condition (25°C / 60% ± 5%RH) and stressed storage condition of (40°C / 75%RH).

Results of photostability testing per ICH Q1B have been presented. Product quality after light exposure in the primary packaging (stoppered and sealed vial) was deemed acceptable.

In conclusion, stability data support a shelf life of 60 months for tisotumab vedotin finished product at the intended storage temperature of 2 - 8°C.

Adventitious agents

Compliance with TSE-Guideline EMEA 410/01 rev03 has been demonstrated. Cells banks have been tested for adventitious and endogenous viruses according to ICH Q5A. Only retrovirus-like particles have been detected which is expected for this type of cells.

Downstream purification steps for virus reduction have been validated. The ability of the purification process to remove virus was evaluated using model viruses. Down-scaling of virus reduction studies has been adequately described. The choice of model viruses and selection of process steps validated for virus reduction is acceptable. Results presented (log reduction factors) are considered acceptable. A sufficient wide safety margin with regard to retroviral particle contamination of the final product has been demonstrated.

2.2.6. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to submission of results of concurrent validation of reprocessing steps and resin lifetime. These points are put forward and agreed as recommendations for future quality development.

2.2.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.8. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

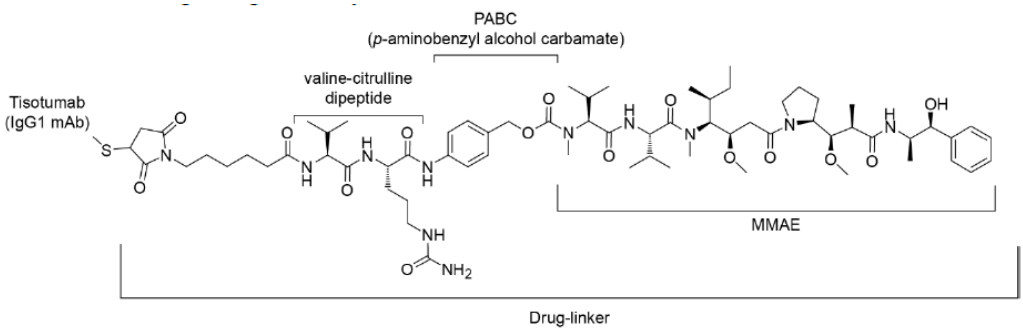
- The applicant is recommended to provide the validation summary of the reprocessing at the virus reduction filtration (VRF) and the bulk fill terminal filtration steps once available.
- The applicant is recommended to provide results of the completed concurrent commercial scale protein A chromatography resin lifetime studies when available.

2.3. Non-clinical aspects

2.3.1. Introduction

Tisotumab vedotin is an antibody-drug conjugate (ADC) composed of a human tissue factor (TF)-specific human monoclonal immunoglobulin G1 (IgG1κ) antibody (tisotumab) chemically conjugated via a protease-cleavable valine-citrulline (vc) linker to the microtubule disrupting agent monomethyl auristatin E (MMAE). The average drug-to-antibody ratio is approximately four.

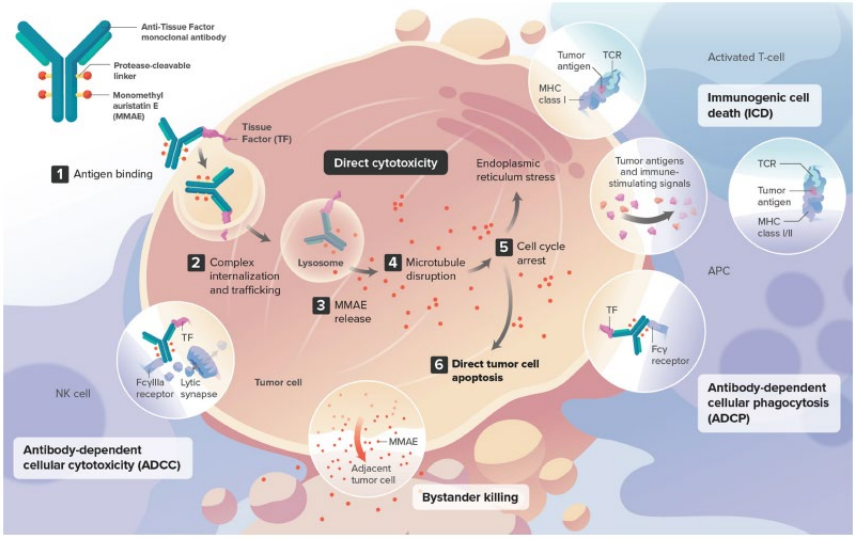
Figure 3 Tisotumab vedotin strcucture



The MMAE portion of tisotumab vedotin is a small molecular entity. Studies of MMAE were conducted to support the marketing application for Adcetris® (brentuximab vedotin) (EMEA/H/C/002455) and is as such considered well characterised. Similar as for Adcetris®, a well-established valine-citrulline dipeptid linker was used for connecting the antibody to the MMAE.

Tisotumab vedotin leverages an elevated TF expression levels on tumour cells to initiate several mechanisms for cell-killing, including MMAE-mediated direct and bystander cytotoxicity, ICD, ADCC, ADCP, and inhibition of TF: activated factor VII (FVIIa)-dependent downstream signalling (Figure 4).

Figure 4 Tumours cell killing pathwas and anti tomour effects of tisotumab vedotin



The indication for tisotumab vedotin is for treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Tisotumab vedotin should be administered intravenously once every three weeks at a dose of 2.0 mg/kg (up to a maximum dose of 200 mg).

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

Primary pharmacodynamic *in vitro* studies for tisotumab vedotin include studies on expression of tissue factor (TF) by different tumour types, target binding characteristics, competition with FVIIa for TF binding, inhibition of TF: FVIIa-mediated intracellular signalling, internalisation characteristics, MMAE-mediated cytotoxicity *in vitro*, induction of immunogenic cell death (ICD), and Fc-mediated effector functions (including ADCC, ADCP and CDC).

Many of the studies were conducted with tisotumab as surrogate for tisotumab vedotin. Furthermore, in many of the study reports several antibodies and ADCs were characterised, however, only results relevant for tisotumab or tisotumab vedotin have been presented and assessed here

In vitro pharmacodynamic studies

Tumour expression of TF

A high prevalence of TF expression was seen in cervical cancer (77%), pancreatic cancer (86%), and glioblastoma (93%) in a study by Genmab investigating TF expression in biopsies from different tumour types using IHC (SR1015-091). For cervical cancers, TF expression was primarily located on the cell membrane. Findings correlated with results from a validation assay study conducted by Ventana Medical Systems (SR1015-178). It should be noted, that the IHC study by Genmab (SR1015-091) was performed using a mouse monoclonal antibody (clone HTF-1) and not tisotumab (HuMax-TF/IgG1-1015-011), as tisotumab was sensitive to TF epitope masking in formalin-fixed paraffin-embedded (FFPE) tissues (but not in frozen sections).

Target binding characterisation

Tisotumab and tisotumab vedotin binding to TF was characterised in an ELISA assay and on the cell-surface of human pancreatic adenocarcinoma (HPAF-II) cells by flow cytometry demonstrating comparable binding characteristics and EC_{50} values (Table 10 below) (GMB1015-083). Affinity and avidity of tisotumab in the low nanomolar range (K_D = 3.2 nM (0.47 µg/mL) and 0.47 nM (0.07 µg/mL), respectively) was measured in a BIAcore assay using human TF (GMB1015-083) and comparable affinity and avidity is expected for tisotumab vedotin.

Table 6: TF-binding characteristics of tisotumab and tisotumab vedotin in vitro

Assay	Source of TF	Tisotumab		Tisotumab Vedotin	
		µg/mL	nM	µg/mL	nM
ELISA	TFECDHis	0.37	2.5	0.47	3.1
Flow cytometry	A431 cells	0.03	0.19	NC	NC
	BxPC-3 cells	0.15	1.01	NC	NC
	MDA-MB-231 cells	0.07	0.46	NC	NC
	HPAF-II cells	0.31	2.1	0.35	2.3
BIAcore	TFECDHis (affinity)	0.47	3.2	NC	NC
	TFECDHis (avidity)	0.07	0.47	NC	NC

ELISA: enzyme-linked immunosorbent assay; NC: not conducted

Human-mouse TF shuffle constructs were made by replacing human domains with murine domains, and expressing them on HEK-293F cells (GMB1015-083). Tisotumab (as surrogate for tisotumab

vedotin) binding was evaluated by flow cytometry and results suggested that amino acids 42-84 were involved in binding of tisotumab to TF.

Effect of tisotumab vedotin on TF:FVIIa binding and downstream signalling

X-ray crystallography (SR1015-191) and structural modelling using PyMOL, revealed a superposition of TF:Fab structure with TF:FVII.The effect of tisotumab and tisotumab vedotin on TF:FVlla binding was studied by non-cell bound TF (ELISA) and cell bound TF (flow cytometry) methods, respectively (GMB1015-085). Furthermore, the effect of tisotumab (as surrogate for tisotumab vedotin) on downstream signalling was studied through measurements of ERK1/2 phosphorylation and IL-8 production (GMB1015-085). Based on the studies, it was shown that tisotumab and tisotumab vedotin dose-dependently inhibited binding of FVIIa to TF (IC_{50} of 0.33-0.45 µg/mL) and that tisotumab (as surrogate for tisotumab vedotin) also inhibited TF:FVIIa-dependent downstream signalling by reducing ERK1/2 phosphorylation and IL-8 production with IC_{50} of 0.12 and 0.78 µg/mL, respectively.

Internalisation characterisation

Internalisation characterisation was done using several different assays, however, only the Fab-TAMRA assays tested both tisotumab vedotin and unconjugated tisotumab.

As an indication of tisotumab-mediated internalisation, flow cytometry was used to measure a reduction in cell-surface TF of 28% and 40% in A431 and SK-OV-3 cell, respectively, upon incubation with tisotumab (GMB1015-087). Presences of tisotumab in the lysosomal compartment was visualised by confocal microscopy showing co-localisation with the lysosomal marker LAMP-1 from 1 h after incubation and onward (GMB1015-087). This finding was confirmed in another assay using tisotumab conjugated with CypHer5E, a pH-sensitive dye which is fluorescent at pH 5.5 (GMB1015-087). Measurements of fluorescence were noted from 1 hour after incubation with increasing intensity over time, indicating internalisation and trafficking to acidic compartments (endosomes or lysosomes). By adding chloroquine, which inhibits endosomal-lysosomal fusion, a reduction in fluorescence were noted, which implied that the majority of the CypHer5E activation was located to the lysosomes.

In the Fab-TAMRA assay (GMB1015-87), anti-human-IgG Fab fragments conjugated with a fluorophore (TAMRA) and a quencher (QSY7) were connected to tisotumab vedotin and tisotumab. Upon internalisation to the endosomes/lysosomes, the quencher dissociates from the fluorophore resulting in fluorescence which are measured by flow cytometry. A fluorescent signal was measured after six hours, indicating that tisotumab vedotin was internalised and trafficked to endosomal/lysosomal compartments. Comparable results were seen for tisotumab and tisotumab vedotin, indicating that vcMMAE-conjugation did not affect internalisation and intracellular trafficking.

MMAE-mediated cytotoxicity of tisotumab vedotin

Direct MMAE-mediated tisotumab vedotin cytotoxicity was shown in an *in vitro* study conducted in 26 human tumour cell lines with varying TF expression, including three cervical cancer cell lines (SiHa, CaSki and ME-180) (GMB1015-087). Tisotumab vedotin showed dose-dependent cytotoxicity in TF-expressing tumour cells with potent cytotoxicity in two out of three of the cervical cell lines (IC_{50} of 1.63 and 7.86 nM for cytotoxicity of CaSki and SiHa cells, respectively). However, results differed for the ME-108 cell line with an IC_{50} of 575.51 nM (as visualised in Figure 11).

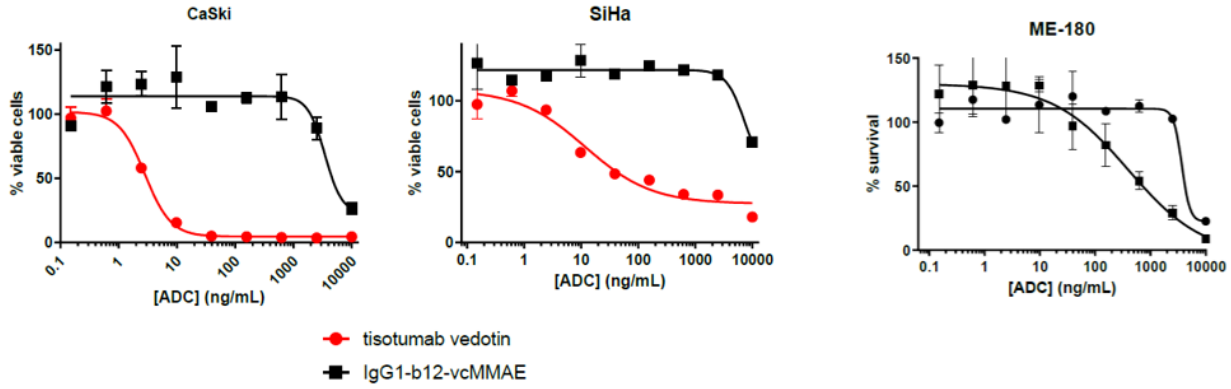


Figure 5*: Cytotoxicity of tisotumab vedotin in the three cervical cancer cell lines*.

Each data point represents the mean ± SD of duplicate wells from one representative experiment. *IC_{50}: 1.63, 7.86 and 575.51 nM for cytotoxicity of CaSki, SiHa and ME-180 cells, respectively (average from three experiments for each cell line).*

Overall for all 26 tumour cell lines, the potency of tisotumab vedotin appeared to be associated with the level of TF expression on the plasma membrane (high TF-expression -> high potency), as shown by quantitative flow cytometry using QIFIKIT analysis (Figure 12 below)

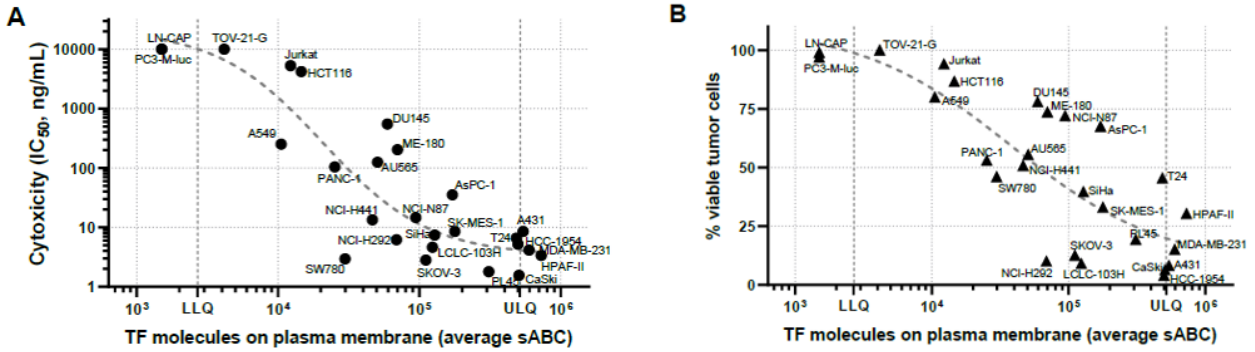


Figure 6 : Association of TF expression level per cell with cytotoxic activity of tisotumab vedotin.

(A) IC_{50} values for tisotumab vedotin mediated tumour cell kill in relation to TF expression levels. (B) Percentage of viable tumour cells after exposure to 100 ng/mL tisotumab vedotin in relation to TF expression levels. In A and B, the dotted line represents the dose-response relationship as estimated by non-linear regression analysis.

A reduction in effect of direct tisotumab vedotin MMAE-mediated cytotoxicity due to the co-presences of the P-glycoprotein efflux pump (P-gp) was shown in TF-expressing A431 cell transfected with P-gp (GMB1015-229).

The effect of tisotumab vedotin MMAE-mediated bystander cytotoxicity was studied in cells with low TF-expression (TF-low cells e.g. Jurkat cells) co-cultured with TF-high cells (e.g. SK-OV-3 cells) (GMB1015-179). Bystander cytotoxicity was observed as cell death in TF-low cells co-cultured with TF-high cells, but not in monoculture of TF-low cells.

Induction of immunogenic cell death by tisotumab vedotin in vitro and in vivo in a mouse xenograft model

Tisotumab vedotin and free MMAE induced hallmarks of immunogenic cell death (ICD) in A431, MDA-MB-231 and HPAF-II cells, including ATP secretion, release of HMGB1, initiation of ER stress response,

activation of innate immune cells by upregulation of monocytes/macrophages, increased activation of T-cells (amplified by concomitant anti-PD-1 treatment) (TRN-5666). *In vitro* findings of ICD were confirmed in a *in vivo* xenograft TF-expressing tumour model in mice (SGN-NC-000451). Tisotumab vedotin upregulated immune-related genes encoding chemokines and type I interferons as determined by RNA sequencing. Additionally, tisotumab vedotin increased recruitment of macrophages and CD11c antigen presenting cells as noted by IHC in the tisotumab vedotin-treated tumours.

Fc-mediated effector mechanisms of tisotumab vedotin

Fc-mediated effector mechanisms of tisotumab and tisotumab vedotin were determined *in vitro* by measuring induction of antibody-dependent cell-mediated cytotoxicity (ADCC) (GMB1015-084) and antibody-dependent cell-mediated phagocytosis (ADCP) (TRN-5631). For the ADCC study, cell lysis of tisotumab-treated ^{51}Cr-labelled TF-expressing target cells (i.e. A431, MDA-MB-231, and BxPC-3) was measured in the presences of human peripheral blood mononuclear cells (PBMCs) with EC_{50} values of 15.4, 8.7, and 4.7 ng/mL, respectively. Comparable results were seen for tisotumab vedotin (only tested in A431 cells),. For the ADCP study, PKH26-labeled TF-expressing cells (BxPC-3 and A431) were incubated for 4 hours with macrophages and opsonised with tisotumab and tisotumab vedotin. Double staining with PKH26 and anti-CD11c antibody was detected by flow cytometry in 30-70% and 20-50% of the total macrophages exposed to tisotumab and tisotumab vedotin, as an indication of dose-dependent phagocytosis. Co-localisation of macrophages and TF-expressing BxPC-3 cells was also visualised by fluorescence microscopy.

In vivo pharmacodynamic studies

Several cell-line derived xenograft (CDX) and patient derived xenograft (PDX) mouse models were constructed to test anti-tumour activity of tisotumab and tisotumab vedotin *in vivo*. Only xenograft models relevant for the current indication of cervical cancer has been assessed in this assessment report. Results from the remaining xenograft models using other cell or tumour types are considered of supportive nature to substantiate overall conclusions..

Anti-tumour activity of monotreatment with tisotumab vedotin in CDX and PDX mouse models in vivo

Anti-tumour activity of tisotumab and tisotumab vedotin was tested in 10 CDX (GMB1015-081/-082/-102/-213) and 21 PDX (GMB1015-148/-149/-210/-211/-212/-223/-224/-225/-226/-227) mouse models *in vivo* using the isotype antibody IgG1-b12, and/or isotype ADC, IgG1-b12-vcMMAE as negative control.

Tisotumab vedotin anti-tumour activity was noted in 6 out of 10 CDX models. In the PDX model, tisotumab vedotin anti-tumour activity were noted in 16 out of 21 models with tumour regression at doses of 4 mg/kg and tumour growth inhibition at doses of 0.5 to 2 mg/kg. For the cervical cancer PDX models, effect of tisotumab vedotin was noted in 5 out of 6 models, primarily at dose of 2-4 mg/kg. Only one study (GMB1015-223) was dedicated to studying the effect of tisotumab vedotin monotherapy in cervical cancer xenograft models, whereas, the remaining results were extracted from studies on combination therapies making transparency difficult.

In general, for all xenograft models, TF expression levels (H-scores) were higher in tisotumab vedotin responding than in non-responding models, although anti-tumour activity were also observed in some xenograft model with low TF expression (GMB1015-228).

Furthermore, a positive effect of tisotumab vedotin on recurrent tumours after initial treatment with tubulin inhibitors (e.g. paclitaxel) were shown in PDX mouse models (GMB1015-148 and GMB1015-149).

Intra-tumoral haemorrhage was observe in 1 CDX lung cancer xenograft model with increasing frequency from doses of 4.5 mg/kg (GMB1015-102) and at high doses (50 mg/kg) in CDX models testing unconjugated tisotumab. As bleeding is considered a potential secondary pharmacological risk, an additional study was conducted to further examine the observed haemorrhage (GMB1015-102). The study showed that intra-tumoral haemorrhage increased in frequency from doses of 4.5 mg/kg in the CDX lung cancer xenograft model (GMB1015-102) and at high doses (50 mg/kg) in other CDX models testing unconjugated tisotumab.

Anti-tumour effect of tisotumab vedotin in combination with other antibody-based therapies or chemotherapy in cervical cancer xenograft models in mice

Studies on combination therapy were assessed in accordance to the applied indication of cervical cancer, remaining studies in other cell or tumour types have not been assessed in this assessment report. Therefore, only results relevant for treatment of cervical cancers were repeated here.

The anti-tumour activity of tisotumab vedotin in combination with bevacizumab, an anti-angiogenic therapy (GMB1015-210), or platinum-based chemotherapy (i.e. cisplatin and/or carboplatin) (GMB1015-211) was tested in cervical cancer PDX xenograft models in mice. The combination of tisotumab vedotin and bevacizumab indicated a small mostly none significant effect on tumour size reduction compared to the best of the single agents in the cervical cancer PDX models (CV1248, CV2320 and CV1802). A tendency towards a prolonged reduction in tumour size were seen for the combination of tisotumab vedotin and bevacizumab.

For combination therapy with tisotumab vedotin and chemotherapy (i.e. cisplatin or carboplatin) in a CV1248 cervical cancer PDX model (CV1248), significant anti-tumour activity with prolonged progression free survival were noted for the tested combination doses (GMB1015-211). However, in the CEFX 633 model similar results were only seen for combination doses of 2-4 mg/kg tisotumab vedotin and 40 mg/kg carboplatin (GMB1015-211). The highest dose of carboplatin of 80 mg/kg shown no effect in combination with tisotumab vedotin in the CEFX 633 model due to the high effect of carboplatin at this dose alone.

2.3.2.2. Secondary pharmacodynamic studies

Tissue factor (TF) is involved in or associated with multiple processes in normal physiology and disease. In general, the majority of those processes can be functionally categorised into either 1) coagulation or 2) signalling pathways dependent on protease-activated receptors (PARs).

Coagulation as a potential secondary pharmacological target

The capacity of tisotumab to interfere with the coagulation pathway was assessed using different coagulation assays including a FXa generation assay (GMB1015-086), a clotting assay or modified PT study (GMB1015-086), a standard PT assay (CRL264005), a thromboelastography (TEG®) assay (HxTFADC-N-Study-Report-0361 and HxTFADC-N-Study-Report-0364), and a thrombin generation assay (TGA) (HxTFADC-N-Study-Report-0361 and HxTFADC-N-Study-Report-0364). In most of these *in vitro* assays tisotumab was used as a surrogate for tisotumab vedotin.

A tisotumab-related inhibition in FXa generation of 19% was measured in a colorimetric assay using recombinant TF pre-incubated in the presence or absence of tisotumab (1.2 - 900 ng/mL) added human FVIIa and recombinant FX in the second incubation step (GMB1015-086).

A prolonged clot formation time of 2.3-fold was seen in the presence of tisotumab (10 mg/mL) in a clotting assay measuring the time-to-clot formation using exogenous TF in human plasma which were re-calcified to initiate coagulation (GMB1015-086). The assay was modified from the principles of the

standard PT study using a 1:1000 dilution of the TF reagent, as no influence of tisotumab or tisotumab vedotin on PT were detected in the commercially available standard PT test using both monkey and human plasma - most likely due to an excess of TF concentration (CRL264005).

An effect on increased clotting time but not clot strength were also noted in two independent TEG assays using LPS-simulated blood from human or monkey donor (HxTFADC-N-Study-Report-0364) or recombinant TF and human whole blood (HxTFADC-N-Study-Report-0361), respectively. In LPS-stimulated whole blood, tisotumab (20 µg/mL) increased clotting time 1.4- to 2.6-fold depending on the donor source, while a 2-fold increase was seen in recombinant TF assay.

In the TAG assay, a reduction of thrombin generation was noted as an increase in lag time in two studies using LPS-simulated blood from human (2.4-fold) or monkey donor (3.6-fold) (HxTFADC-N-Study-Report-0364) or recombinant TF in human whole blood (HxTFADC-N-Study-Report-0361), respectively. The TAG results were tried confirmed using plasma from mouse xenograft models containing human TF bearing microparticle (MP) (HxTFADC-N-Study-Report-0364).

Other potential secondary pharmacological targets

In the literature review provided by the applicant, PAR signalling, embryonic development and ocular tissue was highlighted and discussed as potential secondary pharmacological targets. Additionally, a short overview of TF expression in heathy human adults was also provided.

A tissue cross-reactivity study was conducted with fluorescein marked tisotumab and tisotumab vedotin in a human and cynomolgus monkey tissue panel (study no 20023264). The staining observed was generally consistent with reported sites of TF expression. However, some differences were noted in the tissue staining pattern between human and cynomolgus tissue (see assessment of the study in the toxicology part).

No secondary PD assessment was made for MMAE alone.

2.3.2.3. Safety pharmacology programme

A GLP compliant hERG K+ channels study (CDI129-09-001) was conducted in HEK-293 cells in order to assess the ability of MMAE to block hERG K+ channels in the heart. MMAE was tested at a concentration of 7.18 µg/mL and at a 10-fold higher concentration of 71.8 µg/mL. At 7.18 µg/mL no significant difference was seen to the negative control. At the high concentration of 71.8 µg/mL, a significant difference in mean fractional block of 0.237 ± 0.056 were noted compared to the negative control, but as the differences did not exceed 0.5 the IC_{50} was concluded to be > 71.8 µg/mL. This concentration is approximately 12000-fold higher than the clinically observed C_{max}.

Additionally, safety pharmacology endpoints for tisotumab vedotin representative of the cardiovascular (ECG and heart rate), central nervous (cageside observations) and respiratory systems (breaths per minute) were assessed as part of the repeat-dose toxicity studies as outlined in ICH S9 guideline. No abnormalities on the cardiovascular, respiratory or central nervous systems following tisotumab vedotin administration to cynomolgus monkeys were noted.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed. The omission of these studies is accepted, as there are no drugs anticipated to be co-administered with tisotumab vedotin where a pharmacodynamic interaction is likely to occur.

2.3.3. Pharmacokinetics

The pharmacokinetics and toxicokinetics of tisotumab vedotin, tisotumab, and MMAE were evaluated in exploratory and/or GLP-compliant studies in mice, rats, or cynomolgus monkeys following i.v. administration, the clinically intended route of administration. Methods of detection included immunoassays for antibody analytes in biological matrices and liquid chromatography with tandem mass spectrometry (LCMS/MS) for MMAE. Antidrug antibodies (ADA) were also analyzed to understand the immunogenicity of tisotumab vedotin after multiple doses in cynomolgus monkeys. The distribution, metabolism, and elimination were evaluated for MMAE, the cytotoxic small molecule moiety on tisotumab vedotin. Distribution was evaluated by mass balance studies of tritiated (^{3}H)-MMAE in rats. Hepatocytes and recombinant cytochrome P450s (CYPs) were used for metabolic profiling, metabolite identification, and CYP inhibition and induction studies. In addition, efflux and uptake transporter assays were performed to determine if MMAE was an *in vitro* substrate or inhibitor. The biodistribution of ^{89}Zr-labeled tisotumab was evaluated in cynomolgus monkeys.

2.3.3.1. Analytical methods

Several fully validated methods have been developed to detect the antibody and small molecule components of tisotumab vedotin, including immunoassays for antibody analytes in biological matrices and LC-MS/MS for MMAE in plasma samples. Monomethyl auristatin E concentrations in plasma from rats and cynomolgus monkeys were determined following solid-phase extraction and using a LC/MS/MS method. Furthermore, concentrations of conjugated tisotumab vedotin and total antibody were determined in cynomolgus monkey plasma using an ELISA.

Non-validated methods for analyses of total antibodies and ADAs were developed in support of non-GLP studies.The presence of ADAs against tisotumab vedotin in serum samples from cynomolgus monkeys was furthermore determined using an electrochemiluminescent bridging assay. The method detects ADAs with a sensitivity of 3.55 ng/mL, and drug tolerance at 500 ng/mL ADA was 0.74 µg/mL.

2.3.3.2. Absorption

Table 7 Toxicokinetic data of tisotumab, tisotumab vedotin and MMAE after intravenous repeated doses of tisotumab vedotin to monkeys

Study No/species	Test item	Analyte	Dose (mg/kg)/animals	Study Day	Animal AUC (µg·h/mL)		Cmax (µg/mL)	
					♂	♀	♂	♀
522531/cynomolgus monkeys/5M+5F	Tisotumab vedotin	Tisotumab vedotin (IgG ELISA assay)	1	1	895	1010	28.4	30.9
				85[a]	822	835	14.5	10.8
				85[b]	822	835	14.5	10.8
			3	1	3540	3340	82.9	79.3
				85[a]	2470	3540	55.2	62.0
				85[b]	2470	3540	55.2	62.0
			5	1	4670	7400	114	152
				85[a]	5130	6580	124	149
				85[b]	5060	6580	122	149
		Tisotumab vedotin	1	1	813	781	32.7	28.5
				85[a]	662	659	14.3	9.1

		(MMAE ELISA assay)		85[b]	662	659	14.3	9.1
			3	1	3230	3190	93.2	93.8
				85[a]	2200	3150	55.3	70.0
				85[b]	2200	3150	55.3	70.0
			5	1	5030	6970	150	174
				85[a]	4730	5450	144	161
				85[b]	4470	5450	146	161
		Free MMAE (MMAE ELISA assay)	1	1	5.1×10^{-3}	3.8×10^{-3}	5.4×10^{-5}	$4.3\ 10^{-5}$
				85	4.4×10^{-3}	4.5×10^{-3}	9.7×10^{-5}	14×10^{-5}
			3	1	12×10^{-3}	1.3×10^{-2}	12×10^{-5}	13×10^{-5}
				85	20×10^{-3}	72×10^{-3}	22×10^{-5}	140×10^{-5}
			5	1	23×10^{-3}	21×10^{-3}	24×10^{-5}	21×10^{-5}
				85	35×10^{-3}	1600×10^{-3}	25×10^{-5}	3100×10^{-5}
	Tisotumab	Tisotumab	25	1	50700	50100	729	721
				85	68500	63200	829	826
514850/cynomolgus monkey/2M+2F	Tisotumab	Tisotumab	100 (single dose)	27	146700	129500	2270	2250

Day 85[a] is calculated from all animals. Day 85[b] is from ADA positive animals.

Table 8 Toxicokinetic data of MMAE after intravenous repeated doses of MMAE to rats

Study No/species	Test item	Analyte	Dose (mg/kg)/animals	Study Day	Animal AUC (µg·h/mL)		Cmax (µg/mL)	
					♂	♀	♂	♀
7646-118/Sprague-Dawley rat/10M+10F	MMAE	Free MMAE	0.0097	1	2.6×10^{-3}	2.6×10^{-3}	0.6×10^{-3}	0.5×10^{-3}
				22	4.0×10^{-3}	3.1×10^{-3}	0.7×10^{-3}	0.8×10^{-3}
			0.097	1	25.7×10^{-3}	28.6×10^{-3}	3.5×10^{-3}	3.8×10^{-3}
				22	52.5×10^{-3}	28.6×10^{-3}	5.5×10^{-3}	4.8×10^{-3}
			0.194	1	49.4×10^{-3}	91.0×10^{-3}	5.8×10^{-3}	12.6×10^{-3}
				22	71.0×10^{-3}	49.2×10^{-3}	11.1×10^{-3}	7.0×10^{-3}
8204397/Sprague-Dawley rat/25F	MMAE	Free MMAE	0.2	GD 6	-	16.2×10^{-3}	-	29.7×10^{-3}
				GD 13	-	25.6×10^{-3}	-	50.2×10^{-3}

Tisotumab

Following a single i.v. dose of 1 or 5 mg/kg tisotumab to female BALB/c SCID mice, C_{max} increased in an approximately dose-proportional manner. The volume of distribution was 40 mL/kg and the half-life was greater than two weeks (study No MR1015-143-33).

In the 13-week repeat-dose study in cynomolgus monkeys after tisotumab administration, there was little difference in systemic exposure to tisotumab on Day 1 and 85 between sexes. There was no evidence of accumulation of tisotumab. Anti-drug antibody (ADA) response to tisotumab were limited to two females (one at pretreatment and one on Day 127) (study No 522531).

Tisotumab vedotin

In a single i.v. dose of 1 or 5 mg/kg tisotumab vedotin to female BALB/c SCID mice, C_{max} increased in an approximately dose-proportional manner. The volume of distribution was independent of dose level and was approximately 40 mL/kg. The half-life was determined to ten days (study No MR1015-143-33).

Following tisotumab vedotin dosing in the 13-week repeat-dose study in cynomolgus monkeys, exposure to tisotumab vedotin was comparable when analysed using the IgG or monomethyl auristatin E (MMAE) ELISA assays. On Day 1, systemic exposure increased in a generally dose-proportional manner in males and females. Time to peak plasma concentrations for tisotumab vedotin (median T_{max} estimates) were consistently observed between 0.5 to 0.667 hours for all dose groups, with no apparent changes in mean half-life estimates with increasing dose. Mean half-life ranged from 24 to 50 hours and no substantial systemic accumulation was found for tisotumab vedotin. No comparison following repeat dosing could be made as the majority of animals developed ADA after repeated dosing. Anti-drug antibody positive animals showed a slight decrease in exposure following multiple dose administrations. However, in general, tisotumab vedotin exposures were sufficiently maintained during the treatment period even in the presence of ADA (study No 522531).

Monomethyl auristatin E

After tisotumab vedotin dosing to cynomolgus monkeys for 13 weeks systemic exposure (based on AUC) to free MMAE was generally dose-proportional to dose on Day 1 in males and females up to 5 mg/kg. Exposures to free MMAE were generally comparable between sexes across dose groups and sample days, with the exception of higher levels at 3 and 5 mg/kg in females on Day 64 and 85. Systemic exposure to free MMAE was up to 10^5-fold lower than systemic exposure to tisotumab vedotin. Median T_{max} estimates for free MMAE were 24.5 to 72.5 hours. In some animals that had high ADA titers, a decrease in tisotumab vedotin and an increase in free MMAE in circulation was observed upon subsequent dose administrations (study No 522531).

After dosing of MMAE to rats once weekly for four weeks exposure to free MMAE increased as the dose level increased from 0.0097 to 0.194 mg/kg. The increases in C_{max} were generally less than dose-proportional while the increases in $AUC_{0\text{-}24}$ were generally dose-proportional. No marked (>2-fold) sex differences were observed in C_{max} and $AUC_{0\text{-}24}$ values with the exception of Day 1 where high-dose males showed markedly (>2-fold) lower C_{max} and $AUC_{0\text{-}24}$ values than females. C_{max} and $AUC_{0–24}$ were used to assess accumulation of MMAE, and results indicated a possible change in disposition of MMAE in rat serum after multiple dosing, with a trend for both C_{max} and $AUC_{0\text{-}24}$ to increase with repeated dose administration (study No 7646-118).

After i.v. administration of MMAE at 0.2 mg/kg to pregnant rats, mean C_{max} at GD 6 and 13 in maternal serum were 29.7 and 50.2 ng/mL, respectively. Monomethyl auristatin E was rapidly cleared. MMAE concentrations in amniotic fluid and fetal serum on GD 18 were higher than those in maternal rat serum, indicating that MMAE is highly transferred from maternal rat serum to fetus. Monomethyl auristatin E concentrations in maternal rat serum on GD 18 were below the limit of quantitation for all animals administered 0.2 mg/kg MMAE (study No 8204397).

2.3.3.3. Distribution

Tisotumab and tisotumab vedotin distribution

Biodistribution of ^{89}Zr-labeled tisotumab vedotin and tisotumab was evaluated by whole body PET-CT in mouse xenograft models of TF-expressing tumours (IMA001) and in cynomolgus monkeys (KVU001), respectively. In the mouse xenograft models, a high radioactive uptake was noted in the TF-expressing HPLA tumour compared to the TF-negative PANC-I tumour. Additionally, uptake was observed in spleen (highest level), liver, kidney, heart, lung, stomach, muscle and bone for both ^{89}Zr-tisotumab vedotin and -tisotumab. Conjugation to vcMMAE in ^{89}Zr-tisotumab vedotin appeared to increase liver and kidney uptake by several folds (4- and 2-fold, respectively) compared to ^{89}Zr-tisotumab.

In cynomolgus monkeys, liver and bone marrow received the highest percent (approx. 20% each) of the injected dose of ^{89}Zr-tisotumab and long persistence were noted. Dosimetry measurements in the cynomolgus monkeys showed that kidneys and lower large intestinal wall received the highest dose equivalent of 7.8 and 7.7 rem/mCi of ^{89}Zr-labeled tisotumab. However, high dose equivalents were also noted in the liver, gallbladder wall and testes (5.5, 5.3 and 4.9 rem/mCi, respectively).

Monomethyl auristatin E (MMAE) distribution

Quantitative whole-body autoradiography in male Long-Evans rats dosed i.v. with 0.056 mg/kg ^{3}H-MMAE (study no. 96D-1201), showed a wide organ distribution of ^{3}H-MMAE with tissue concentrations higher than blood. The highest ^{3}H-MMAE concentration was demonstrated in relation to bile, content of alimentary tract and urinary bladder. Organ concentrations of >0.20 µg eq/g at C_{max} were found in the anterior pituitary gland, lung and cortex and medulla of the kidney. ^{3}H-MMAE radioactivity was eliminated in most tissues by 96 h post dose, except for thymus, anterior and posterior pituitary glands, and eye uveal tract. A lack of elimination from the eye uveal tract were noted in rats, as the only organ above the quantitation limit at 672 hours post dose. Distribution to the brain was assessed and small amounts of ^{3}H-MMAE (0.134 µg eq/g) was measured only in the choroid plexus, whereas, no measurable amounts were detected in cerebellum, cerebrum or medulla.

Plasma protein binding of ^{3}H-MMAE was evaluated *in vitro* by liquid scintillation counting methods in plasma samples from mouse, rat, cynomolgus monkey and human added 1, 10 and 100 nM of ^{3}H-MMAE (XS-0025) at 37°C. Results demonstrated a high plasma protein binding of ^{3}H-MMAE in humans (67.9-82.2%) and rats (72.0-73.5%) compared to cynomolgus monkey (17.1-18.9%) and mice (18.8-28.5%). Concentration-dependent protein binding appeared in human and mouse but not in rat and cynomolgus monkey.

The blood cell partitioning potential of ^{3}H-MMAE was evaluated in blood samples from mouse, rat, cynomolgus monkey and human after incubation for 1 h at 37°C at concentrations of 2, 20, 200, 1000 and 5000 nM ^{3}H-MMAE. Blood to plasma (B/P) ratio was calculated based on the ratios of radioactivity in whole blood and plasma, respectively (14-0271-GNE-A1). MMAE showed species-dependent red blood cell (RBC) partitioning with blood to plasma concentration ratios >1 in mouse, rat, and monkey blood at clinically relevant concentrations of 2 and 20 nM, but <1 in human blood, indicating a very low RBC partitioning in humans.

MMAE crosses the placenta and was measurable in foetal serum, as shown in the conducted EFD study (study No 8204397). No study on excretion to milk has been submitted.

2.3.3.4. Metabolism

In vitro

In vitro metabolism studies of MMAE with rat, monkey and human hepatocytes identified twelve metabolites. All metabolites detected in human hepatocytes were also detected in rat and/or cynomolgus monkey hepatocytes (study No XT084007). In another study human liver microsomes converted ^{3}H-MMAE into eight metabolites similar to those formed in rat and monkey hepatocytes including three major metabolites C4, C7 and C8 formed by CYP3A4 (study No XT084006).

In vivo

Unchanged ^{3}H-MMAE was demonstrated to be the primary molecular species excreted in rat urine and faeces in an *in vivo* metabolite profiling study using HPLC radiometric/UV detection for metabolite determination and LC-MS/MS for identification (Study no. 420501). In faeces, a second radiolabelled metabolite was identified as O-desmethylMMAE (C4) (maximum of 17.1-25.3% of total MMAE at 12-24 h). C4 is a metabolite of the parent drug and is as such considered toxicological qualified. In urine, two additional metabolites were observed only in male animals but not identified due to low abundance (2.87% and 1.03%, respectively). When compared to the human metabolite profile (CPH-SGN-35-001), the study in rats only provided limited information, as it only covered one of four metabolites in human faeces and none of the metabolites found in human urine. -

No *in vivo* studies were conducted to detect metabolites in plasma in neither rats nor cynomolgus monkeys.

2.3.3.5. Excretion

No excretion studies were expected for the antibody moiety of tisotumab vedotin in accordance to ICH S6(R1) guideline, as antibodies are fully degraded in the body. Only MMAE excretion data was provided. The data submitted has been conducted for the MAA of brentuximab vedotin, as they share the same linker-drug conjugate (vcMMAE).

A GLP-compliant mass balance excretion study (study no. 420501) was performed in rats following a single i.v. dose of ^{3}H-MMAE. The major route of excretion in rats was via faeces (96.7 to 101.8 %), with urinary excretion accounting for <15% of the dose. Unchanged ^{3}H-MMAE was the predominant component excreted in both urine and faeces. Approximately 90-95% of the ^{3}H-MMAE was excreted within the first 48h and the half-life was 1 to 2.3 days in rats.

2.3.3.6. Pharmacokinetic drug interactions

In vitro pharmacokinetic drug interactions were assessed with MMAE.

Inhibitor/inducer of CYP enzymes

Monomethyl auristatin E (MMAE) is not a potent reversible inhibitor (study No XT085021) or inducer (study No XT133043) of CYP3A4/5, but it is a quasi-irreversible, metabolism-based CYP3A4/5 inhibitor. Low MMAE serum C_{max} (8.23 nM or 5.91 ng/mL) and high kinetic interaction coefficient (1.12 µM) was seen in humans in study No SR1015-248

Transporter interaction

Several *in vitro* assays were conducted to assess MMAE as a substrate or an inhibitor of efflux and uptake transporters P-gp, BCRP, BSEP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1 or OATP1B3 (study Nos XT108004, RPT-01709, PDM-0008, PDM-0009, PDM-0010, PDM-0011, PDM 0012 and 15-3234).

From these studies it was concluded that:

- Monomethyl auristatin E is a substrate of P-gp.

- Monomethyl auristatin E is not a substrate of BCRP, MRP2, OCT2, OAT1, OAT3, OATP1B1 or OATP1B3.
- Monomethyl auristatin E is not an inhibitor of P-gp, BCRP, BSEP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1 or OATP1B3 at clinically relevant concentrations.

2.3.3.7. Other pharmacokinetic studies

Tisotumab vedotin was stable at 37°C in human and cynomolgus K_2EDTA plasma over a 14-day incubation period.

2.3.4. Toxicology

The toxicity of tisotumab, tisotumab vedotin, monomethyl auristatin E (MMAE) and h00-1006(4) was evaluated in repeat-dose GLP-compliant studies in cynomolgus monkeys (all components) and rats (MMAE only). Tissue cross-reactivity of tisotumab vedotin was characterised in a panel of tissues from cynomolgus monkeys and humans. Embryo-foetal development studies were only conducted with MMAE. The genotoxic potential of MMAE alone was studied in a standard test battery (bacterial and mammalian cell *in vitro* assays and *in vivo* micronucleus assay).

2.3.4.1. Single dose toxicity

Single-dose toxicity studies of MMAE were performed in rats and cynomolgus monkeys.

Table 9 Single-dose toxicity studies with MMAE

Study details	**No:Group**	**Dose (mg/kg)**	**Major (alt. Salient) findings**
Single-dose toxicity studies (MTDs highlighted)			
Sprague-Dawley rat i.v. non-GLP (R-Tox-15)	Vehicle: 2M/2F Dosed: 3M/3F	0 0.01 0.1 0.2	*Mortality*: All rats treated with 0.2 mg/kg MMAE were euthanised two days postdose. Bone marrow cytology at 0.1 mg/kg: Erythroid hyperplasia accompanied by mild cellular lysis. *Histopathology*: Thymus (lymphoid depletion) and liver (single cell necrosis and biliary hypoplasia). Target organs: Bone marrow and liver. **NOEL: 0.01 mg/kg.**
Sprague-Dawley rat i.v. non-GLP (R-Tox-33)	3F	0.2	*Mortality*: 3/33 rats died 3 to 4 days postdose. *Clinical pathology*: Reductions in total leukocytes (predominantly neutrophils) from 2 to 5 days postdose, with recovery by 7 to 8 days postdose; decrease in erythrocyte mass from 2 to 8 days postdose, with recovery by 14 days postdose. *Histopathology*: Bone marrow (pancytopenia from 2 to 5 days postdose with a rapid regenerative recovery). **MTD: Not determined.**
Sprague-Dawley rat i.v. non-GLP (MPI1019-001)	4M/4F	0 0.05 0.25	*Clinical pathology*: ↓Red cell parameters. ↑ALP. *Histopathology*: Sternal bone marrow (atrophy), thymic (necrosis/atrophy), gastrointestinal (epithelial single cell necrosis) and hepatic (subacute inflammation). *Target organs*: Bone marrow, thymus, GI-tract and liver. **Observed maximum non-lethal dose: 0.25 mg/kg.**

Cynomolgus monkey i.v. non-GLP (SNBL163.19)	Main: 1M/1F	0.116	**0.116 mg/kg** *Mortality*: 1M: on Day 28 postdose. Macroscopic changes consisted of an abscess of the right lung and a light grayish to tan coloration of the left cranial lobe. Abscess formation indicated a likelihood of a primary or secondary bacterial infection and pneumonia. The lung lesions/pneumonia were the likely cause of death. ↓*BW.* *Clinical observations*: Hunched posture and dry or hard faeces. *Haematology*: ↓White blood cells, red blood cell, haemoglobin, haematocrit and reticulocyte. *Clinical chemistry*: ↓Albumin. ↑AST. *Histopathology*: No necropsies were performed. **NOAEL: Not determined.**

Administration of a single i.v. dose of MMAE to rats led to mortality at 0.2 mg/kg. Monomethyl auristatin E caused bone marrow suppression (neutropenia) and peripheral blood cell changes (low red blood cell mass), thymic atrophy, gastrointestinal tract and liver toxicity (study Nos R-Tox-15, R-Tox-33 and MPI1019-001).

A single i.v. dose of MMAE at 0.116 mg/kg to cynomolgus monkeys was poorly tolerated with mortality in the male animal and changes in clinical observations, body weights, haematology (decrease in red and white blood cells) and serum chemistry (decrease in albumin and elevation in AST) parameters. No necropsies were performed (study No SNBL163.19).

2.3.4.2. Repeat dose toxicity

Tisotumab

Repeat-dose toxicity study with tisotumab were performed in cynomolgus monkeys.

Table 10 Repeat-dose toxicity studies with tisotumab

Study details	No:Group	Dose (mg/kg)	Exposure		Major findings & NOAEL
			Cmax µg/mL	AUC µg/mL/h	
Cynomolgus monkey 4 + 0 w (escalating single dose Q1Wx3) i.v. Non-GLP (514850)	Main: 2M+2F	0	-	-	**≤100 mg/kg** Well-tolerated. **NOAEL: N/A**
		1	24	1006	
		10	214	13505	
		100	2260	138100	
Cynomolgus monkey 13 + 6 w QWx3 i.v. GLP (522531)	Main: 5M+5F Recovery: 2M+2F	0	-	-	**25 mg/kg** *Coagulation*: M+F: Prolonged prothrombin times (<20% control) throughout the treatment periods. *Ophthalmoscopy*: M: Mild effect on the fundus of the eye. Recovery: M+F: Prolonged prothrombin times. **NOAEL: 25 mg/kg**

In the GLP compliant 13-week repeat-dose study in cynomolgus monkeys the unconjugated antibody tisotumab appeared well tolerated at doses up to 25 mg/kg and not associated with signs of toxicity. Glassy appearance of the fundus in both eyes was observed in all males and prothrombin time was prolonged throughout the treatment period (study No 522531).

Tisotumab vedotin

One dose-range finding study and one pivotal repeat-dose toxicity study with tisotumab vedotin were performed in cynomolgus monkey.

In a 10-week non-GLP dose-range finding study with a 6-week recovery period, tisotumab vedotin was administered i.v. at doses of 1, 3 or 6/5 mg/kg every three weeks on four occasions to cynomolgus monkeys (study No 521988). One female dosed at 6 mg/kg was euthanised on Day 11 due to adverse clinical signs. The animal experienced abnormal respiration (shallow, laboured breathing, gasping and wheezing). Clinical pathology investigations before necropsy revealed: Decreases in red blood cell mass, neutrophil and total leukocyte counts and increases in reticulocyte and platelet counts. In this study the primary target organs identified with tisotumab vedotin were the skin and bone marrow. Haematological changes were similar to findings in the 13-week repeat-dose study. At recovery necropsy there were no histopathological findings related to tisotumab vedotin.

Overall, exposure was evident in all animals after the first dose administration and was dose-dependent. In the majority of animals, exposure after repeated dose administration was reduced or even abolished due to the generation of anti-drug antibodies (ADA) (study No 521988).

In a 13-week GLP repeat-dose study with a 6-week recovery period tisotumab vedotin was administered i.v. at doses of 1, 3 or 5 mg/kg every three weeks on five occasions to cynomolgus monkeys. An interim necropsy group designed to investigate skin toxicity, skin biopsies were obtained between Days 6 to 12 after a single dose of 4 mg/kg. The primary target organs identified for tisotumab vedotin were skin, bone marrow, eyes and male reproductive organs.

In most cases, initial skin reaction was primarily observed as reddening of the skin on the femoral or chest areas that progressed to dry flaky skin. Other areas of the body surface were also affected. The skin reactions generally reversed within approximately 14 days. However, severe adverse skin reactions in three animals at the 5 mg/kg dose prompted unscheduled euthanasia. Skin histopathology from the interim study group at 4 mg/kg identified the following: Ulcerative dermatitis, mixed subepidermal inflammatory cell infiltration, epidermal hydropic degeneration/hyperplasia and haemorrhage (subcutis) from affected skin regions. The findings at 4 mg/kg were considered less marked than those observed in the premature decedents at 5 mg/kg. The 3 mg/kg dose level showed less severe findings with reversibility occurring before the next dose administration.

Bone marrow effects included decreased granulopoiesis and cellularity associated with decreased peripheral red blood cell mass and suppression of leukocytes and neutrophils at 3 or 5 mg/kg which showed reversibility during the recovery phase.

The majority of animals administered 5 mg/kg tisotumab vedotin had clinical observations that included reddened eye(s), reddened or swollen conjunctiva (with or without discharge), swollen upper eyelid, partially closed eye, swelling to eyelid with discharge and/or conjunctivitis. Ophthalmoscopic examination of male cynomolgus monkeys treated with 5 mg/kg indicated an effect on the fundus, which appeared glassy. No ocular changes were seen upon recovery.

Male reproductive changes consisted of seminiferous tubular atrophy in the testes and absence of sperm, decreased sperm content and epithelial vacuolation in the epididymides. The changes were associated with decreased testicular size, reduced or total absence of sperm counts and sperm motility observed at 1, 3 or 5 mg/kg corresponding to approximately 0.5- to 4-fold the human systemic exposure (based on AUC) at the clinically recommended dose. Partial recovery of the findings in testes and epididymides were noted at 3 and 5 mg/kg and full recovery at 1 mg/kg after a 6-week recovery period.

Anti-drug antibodies were formed in a large number of tisotumab vedotin-treated animals in the study however, exposures were sufficiently maintained during the treatment period.

Monomethyl auristatin E

Table 11 Repeat-dose toxicity studies with MMAE

Study details	**No:Group**	**Dose (mg/kg)**	**Exposure**		**Major findings & NOAEL**
			Cmax ng/mL	**AUC ng/mL/h**	
Sprague-Dawley rat 4 +2 w Q1Wx4 i.v. Non-GLP (R-Tox-13)	Main: 5M/5F (control: 2M+2F) Recovery: 2M+2F	0	-	-	**≥0.097 mg/kg** *Clinical observations:* M+F*:* Piloerection. *Haematology:* ↓White blood cells.
		0.0097	-	-	**0.097 mg/kg** *Haematology*: F: ↓Neutrophils.
		0.097	-	-	**0.29 mg/kg** *Mortality*: All male rats. M+F: ↓*BW*. *Haematology*: M+F: ↓ Erythrocyte, haemoglobin and haematocrit. F: ↓ Leukocytes and platelets. *Clinical chemistry*: ↑AST, ALT, total bilirubin, GGT, ALP, total protein, cholesterol and ↓albumin. *Histopathology*: Bone marrow (depletion), liver (necrosis and biliary hyperplasia), spleen (atypical mitosis).
		0.29	-	-	Recovery: **0.0097 mg/kg** *Haematology*: M: ↓Neutrophils **≤0.29 mg/kg** *Clinical chemistry*: All but the cholesterol levels. **0.29 mg/kg** *Histopathology*: M+F: Liver (necrosis). **NOAEL: 0.0097 mg/kg.**

Sprague-Dawley rat 4 + 4 w Q1Wx4 i.v. GLP (7646-118)	Main: 15M+15F (10M+10F low dose MMAE group) Recovery: 5M+5F (no low dose MMAE group) TK: 10M+10F	0	-	-	**0.097 mg/kg** M: ↓BW gain. *Haematology*: M+F: ↓Reticulocyte, erythrocyte, haemoglobin and haematocrit. ↑MCV and MCH. *Clinical chemistry*: M+F: ↓Albumin and albumin A/G ratio. *Organ weight*: M+F: ↓Thymus. **0.194 mg/kg** M: ↓*BW* and *BW gain*. *Haematology*: M+F: ↓Reticulocyte, red blood cell count, haemoglobin and haematocrit. ↑MCV and MCH. F: ↑platelet, M+F: ↓White blood cell count, neutrophil, lymphocyte, eosinophil and monocyte. *Coagulation*: M+F: ↓APTT. *Clinical chemistry*: M+F: ↑Glu, ↓prot, ↓ALP and ↑GGT. M+F: ↑chol. M: ↑bil and AST. *Organ weight*: ↓Testes and M+F: ↓Thymus *Histopathology*: M+F: Thymus (lymphocytic depletion) and bone marrow (hypocellularity). F: Thymus (lymphocytic necrosis). M: Testis (tubules with decreased spermatocytes) and liver (minimal coagulative necrosis). Recovery: **≥0.097 mg/kg** *Haematology*: F: ↓Erythrocyte. M+F: ↑MCV and MCH. *Coagulation*: M: ↓APTT. *Clinical chemistry*: M: ↑Chol. **0.194 mg/kg** *Organ weight*: ↓Testes and epididymides. *Histopathology*: Testes (diffuse seminiferous tubular degeneration, Sertoli cell vacuolation and reduced spermatogenesis) and epididymides (aspermia). **NOAEL: 0.0097 mg/kg.**
		0.0097	**0.77**	**3.53**	
		0.097	5.17	40.53	
		0.194	9.03	60.09	
Cynomolgus monkey 6 + 0 w Q3Wx2 (0.058 mg/kg) i.v. non-GLP (SNBL163.19)	Main: 1M/1F	0.058	-	-	**0.058 mg/kg** *Clinical observations*: Hunched posture. *Haematology*: ↓White blood cells (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), erythrocytes, haemoglobin, haematocrit and reticulocyte. *Clinical chemistry*: ↓Albumin. ↑AST. *Histopathology*: No necropsies were performed. **NOAEL: Not determined.**
Cynomolgus monkey 11 + 5 w 3Q4W i.v. GLP (SNBL163.16)	Main: 4M+4F (control group) and 3M+3F (MMAE group) Recovery: 2M+2F	0	-	-	**0.058 mg/kg** *Haematology:* M+F: ↓White blood cell, lymphocyte, reticulocyte, MCV, MCH, eosinophil. and neutrophil. *Histopathology*: M+F: Bone marrow (hypocellularity), thymus (lymphoid depletion) and spleen (lymphoid depletion). **NOAEL: Not determined.**
		0.058	-	-	

Non-binding control ADC h00-1006(4)

Table 12 Repeat-dose toxicity study with non-binding control ADC h00-1006(4)

Study details	No:Group	Dose (mg/kg)	Exposure (analyte acMMAE)		Major findings & NOAEL
			Cmax ng/mL	AUC ng/mL/h	
Cynomolgus monkey 4 + 4 w Q1Wx4 i.v. GLP (163.66)	Main: 3M/3F Recovery: 2M/2F	0			**3 mg/kg** *Haematology*: M+F: ↓Haemoglobin, red blood cells, haematocrit, reticulocyte, white blood cells, lymphocyte, neutrophil and eosinophil. ↑Platelet and red blood cell distribution width. *Organ weights*: M+F: ↓Thymus. *Histopathology*: M+F: Bone marrow (decreased cellularity), spleen decreased germinal centers) and thymus (lymphocyte depletion). F: Ovary (reduced secondary and tertiary follicles). **4 mg/kg** *Haematology*: M+F: ↓Haemoglobin, red blood cells, haematocrit, reticulocyte, white blood cells, lymphocyte, neutrophil and eosinophil. ↑Platelet and red blood cell distribution width. *Coagulation*: F: ↑Fibrinogen. *Organ weights*: M+F: ↓Thymus. *Histopathology*: M+F: Bone marrow (decreased cellularity), spleen decreased germinal centers) and thymus (lymphocyte depletion). F: Ovary (reduced secondary and tertiary follicles). **5 mg/kg** *Haematology*: M+F: ↓Haemoglobin, red blood cells, haematocrit, reticulocyte, white blood cells, lymphocyte, neutrophil and eosinophil. ↑Platelets and red blood cell distribution width. *Clinical chemistry*: F: ↑C-reactive protein and globulin. M: ↓Albumin and M+F: ↓Albumin/globulin ratio. *Coagulation*: F: ↑Fibrinogen. *Organ weights*: M+F: ↓Thymus. *Histopathology*: M+F: Bone marrow (decreased cellularity), spleen decreased germinal centers) and thymus (lymphocyte depletion). F: Ovary (reduced secondary and tertiary follicles). Recovery: **3 mg/kg** *Coagulation*: F: ↑Fibrinogen. *Organ weights*: F: ↓Thymus. *Histopathology*: M+F: Spleen findings (decreased germinal centers had partially reversed). Ovarian changes (partial recovery). **4 mg/kg** *Organ weights*: F: ↓Thymus. *Histopathology*: Ovarian changes (partial recovery) and M+F: Spleen findings (decreased germinal centers had partially reversed).

					5 mg/kg *Organ weights*: M+F: ↓Thymus. *Histopathology*: Ovarian changes (partial recovery). M: Thymus (decreased lymphocytes). M+F: Spleen findings (decreased germinal centers had partially reversed). **NOAEL: N/A.**

Non-binding control antibody-drug conjugate h00-1006(4) was administered i.v. to cynomolgus monkeys at doses of 3, 4, or 5 mg/kg in a GLP-compliant 4-week repeat-dose toxicity study with a 4-week recovery period and resulted in toxicity in the bone marrow (decreased cellularity), spleen (decreased germinal centers), thymus (lymphocyte depletion) and ovary (reduced secondary and tertiary follicles). All findings, except decreased thymus size, were partially or fully reversed after the recovery period. The findings were consistent with the mechanism of action of MMAE (study No 163.66).

2.3.4.3. Genotoxicity

Table 13 Overview of genotoxicity studies of MMAE

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results positive/negative/equivocal**
Gene mutations in bacteria/study No AA66EH.503.BTL/GLP	*Salmonella typhimurium* and *Escherichia coli* strains: TA98, TA100, TA1535, TA1537 and WP2 uvrA	75, 200, 600, 1800, and 5000 µg/plate/+/- S9 Solvent: DMSO	Negative
Gene mutations in mammalian cells/study No 8204155/GLP	Mouse lymphoma L5178Y $TK^{+/-}$ cell line	Up to 70 ng/mL (+S9) Up to 15 ng/mL (-S9)	Negative
Chromosomal aberrations in vivo/study No 8204151/GLP	Rat, micronuclei in bone marrow (n = 5 male Sprague-Dawley rats/group)	0 (vehicle), MMAE: 0.01, 0.1 or 0.2 mg/kg i.v. Cyclophosphamide (positive control): 60 mg/kg by oral gavage,	Positive: Statistically significant increases in micronucleated polychromatic erythrocytes at doses of 0.1 and 0.2 mg/kg. Predominant formation of micronuclei with $centromere^{+}$ indicated an aneugenic mode of action. MMAE was cytotoxic to the bone marrow (i.e. a statistically significant decrease in the PCE:NCE ratios) at 0.2 mg/kg.

Genotoxicity studies used monomethyl auristatin E (MMAE) rather than tisotumab vedotin. The genotoxic potential was sufficiently studied in a standard test battery comprising of GLP-compliant *in vitro* bacterial and mammalian cell assays and an *in vivo* micronucleus assay. Monomethyl auristatin E was negative in a reverse mutation test in bacteria (Ames test) and in a L5178Y thymidine $kinase^{+/-}$ mouse lymphoma mutation assay. However, MMAE was positive for genotoxicity in the *in vivo* rat bone marrow micronucleus study through an aneugenic mechanism.

2.3.4.4. Carcinogenicity

No carcinogenicity studies have been performed.

2.3.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development

Fertility and early embryonic development studies were not conducted. However, testicular and ovarian toxicity were evaluated in the repeat-dose studies.

Embryo-foetal development

Table 14 Overview of embryo-foetal study of MMAE

Study details		**No:Sex/ Group**	**Dose** (mg/ kg) Q7D × 2	**Exposure**		**Major (all salient) findings & NOAEL**
				Cmax ng/mL (GD 6)	**Cmax** ng/mL (GD 13)	
	Embryo-foetal toxicity studies (NOAELs highlighted)					
Sprague-Dawley rat GD 6-13 i.v. GLP (8204397)		25F	0	-	-	**F0** ↓BW. Haematological decrements. Thymus (lymphocyte depletion). Increase in splenic extramedullary haematopoiesis. Sternal bone marrow (hypercellularity). Abortion/resorption 1/24. **F1** ↑Resorptions. ↑Post implantation loss. ↑Early delivery. ↓Viable foetuses. ↑External malformations. **The NOAEL could not be determined**.

A GLP-compliant embryo-foetal development study was conducted with MMAE but not with tisotumab vedotin. Administration of 0.2 mg/kg MMAE to rats resulted in adverse embryo-foetal toxicities: Increases in total resorptions, post-implantation loss, early delivery, loss of viable foetuses and foetal external malformations (study No 8204397).

Prenatal and postnatal development, including maternal function

Prenatal and postnatal development studies were not conducted.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No juvenile studies were submitted.

2.3.4.6. Interspecies comparison and exposure margins to clinical exposure

Table 15 Interspecies comparison of tisotumab vedotin exposure

Study ID/ species	Test item	Dose association	Dose level (mg/kg)	C_{max} (µg/mL)		Animal AUC (µg.h/mL)		Animal:Human[a] Exposure Multiple			
								C_{max}		AUC	
				♂	♀	♂	♀	♂	♀	♂	♀
522531/ cynomolgus monkey	Tisotumab vedotin	NOAEL	1[b,c]	-	10.8	-	835	-	0.26	-	0.60
					9.1		659	-	0.22	-	0.48
		N/A	1[b,c]	14.5	-	822	-	0.36	-	0.59	-
				14.3		662		0.35		0.48	
		HNSTD	3[b]	55.2	62.0	2470	3540	1.35	1.52	1.79	2.56
				55.3	70.0	2200	3150	1.36	1.72	1.59	2.28
		N/A	5[b]	124	149	5130	6580	3.04	3.65	3.71	4.76
				144	161	4730	5450	3.53	3.95	3.42	3.94
SR1015-248/Human	Tisotumab vedotin	Recommended clinical dose	2	40.8		1382		-	-	-	-

[a] Predicted adult human exposure of tisotumab vedotin following 2.0 mg/kg Q3W (recommended clinical dose) dosing with tisotumab vedotin: C_{max} = 40.8 µg/mL and AUC = 1382 µg×h/mL (study No SR1015-248).
[b] Values derived from two assays (IgG and MMAE ELISA).
[c] NOAEL for males <1 mg/kg.

Table 16 Interspecies comparison of MMAE exposure

Study ID/ species	Test item	Dose association	Dose level (mg/kg)	C_{max} (ng/mL)		Animal AUC (ng.h/mL)		Animal:Human[a] Exposure Multiple			
								C_{max}		AUC	
				♂	♀	♂	♀	♂	♀	♂	♀
7646-118/ Sprague-Dawley rat	MMAE	NOAEL	0.0097	0.70	0.84	3.98	3.07	0.12	0.14	0.003	0.003
		HNSTD	0.194	11.05	7.01	70.99	49.18	1.84	1.17	0.02	0.06
522531/ cynomolgus monkey	Tisotumab vedotin	NOAEL	1	-	0.14	-	4.5	-	0.02	-	0.003
		N/A	1	0.10	-	4.4	-	0.02	-	0.004	-
		HNSTD	3	0.22	1.4	20	72	0.04	0.23	0.016	0.06
		N/A	5	0.25	31	35	1600	0.04	5.2	0.029	1.32
SR1015-248/Human	Tisotumab vedotin	Recommended clinical dose	2	5.99		1214		-	-	-	-

[a] Predicted adult human exposure of MMAE following 2.0 mg/kg Q3W (recommended clinical dose) dosing with tisotumab vedotin: C_{max} = 5.99 ng/mL and AUC = 1214 ng×h/mL (study No SR1015-248).

Interspecies comparison data of tisotumab vedotin were presented as a comparison of exposures (C_{max} and AUC) from the 13-week repeat-dose cynomolgus monkey study (study No 522531) with predicted adult human exposure at the clinical dose of 2.0 mg/kg administred once every three weeks (clinical study No SR1015-248).

The systemic exposure (C_{max} and AUC calculated from all animals on Day 85) at the NOAEL of 1 mg/kg administred once every three weeks in the 13-week repeated-dose toxicity study in female cynomolgus monkeys was 10.8/9.1 µg/mL and 659/835 µg×h/mL (values were derived from two assays), respectively. Based on the C_{max} and AUC, the NOAEL dose provided approximately 0.26 to 0.22- and 0.48 to 0.60-fold exposure margins over the predicted adult human exposure following multiple dosing with tisotumab vedotin. The NOAEL for males was <1 mg/kg. The applicant also provided exposure (C_{max} and AUC) ratios between monkey and human at the highest non-severely toxic dose of 3 mg/kg, which was approximately 1.35- to 2.56-fold that in humans. The highest tisotumab vedotin exposures achieved in cynomolgus monkey at 5 mg/kg exceeded the clinical exposure and supported the relevance of the results for evaluating clinical safety. Low exposure margins were seen when comparing systemic exposure of MMAE of rat and monkey to human.

2.3.4.7. Toxicokinetic data

Toxicokinetics of tisotumab, tisotumab vedotin and MMAE were assessed in section Absorption.

2.3.4.8. Local tolerance

Microscopic evaluation of the injection site as part of the repeat-dose toxicology studies in both rats (study No 7646-118) and monkeys (study Nos 163.16 and 522531) identified no tisotumab-, tisotumab vedotin- or MMAE-related effects.

2.3.4.9. Other toxicity studies

2.3.4.9.1. Antigenicity

No stand-alone antigenicity study of tisotumab or tisotumab vedotin was conducted. Formation of anti-drug antibodies (ADA) against tisotumab (study Nos 522531 and 514850) or tisotumab vedotin (study Nos 522531 and 521988) and its impact on toxicokinetics was assessed based on data from i.v. repeat-dose toxicity studies in cynomolgus monkeys. Most monkeys developed ADAs following repeated doses of tisotumab vedotin. In the 10- and 13-week study ADAs were formed in a large proportion of tisotumab vedotin-treated monkeys. In the 13-week study tisotumab vedotin exposures were sufficiently maintained during the treatment period. In some animals that had high ADA titers, a decrease in tisotumab vedotin and an increase in free MMAE in the circulation was observed upon subsequent dose administrations. In the 10-week study exposure after multiple doses was reduced or even abolished due to the generation of ADAs. Following repeated administration of tisotumab, ADA formation was observed in two monkeys in the 13-week study and no ADAs against tisotumab were detected in the 4-week study.

2.3.4.9.2. Immunotoxicity

Immunotoxicity evaluations were incorporated in the repeat-dose toxicity studies.

2.3.4.9.3. Dependence

No studies were submitted.

2.3.4.9.4. Studies on metabolites

No studies on metabolites were presented.

2.3.4.9.5. Studies on impurities

No data on impurities were presented in the toxicology part of the dossier.

2.3.4.9.6. Phototoxicity

In a non-GLP study (study No TRN-2926-A), MMAE and valine-citrulline-MMAE were adequately evaluated for potential phototoxicity risks according to the principles outlined in ICH guideline S10. None of the compounds had absorbances in the range of natural sunlight that exceeded the defined threshold for potential phototoxic concern.

2.3.4.9.7. Excipients studies

No data on excipients were presented in the toxicology part of the dossier.

2.3.4.9.8. Other (toxicity) studies (including mechanistic studies)

Immunohistochemistry, flow cytometry and/or ELISA showed that tisotumab was cross-reactive with cynomolgus monkey and human tissue factor (TF) but not with dog, pig, rabbit, rat or mouse. Hence, cynomolgus monkey was selected as the relevant species (study No GMB1015-088).

In a GLP-compliant study tisotumab and tisotumab vedotin tissue cross-reactivity were further assessed in a panel of human and cynomolgus monkey tissues. The staining observed was generally consistent with reported sites of TF expression and was generally observed both on the cell membrane and in the cytosol. Test article stained tissue elements that were observed in the cynomolgus monkey but not in the human tissues included mesothelium in several cynomolgus monkey tissues, endothelium in the spleen, and thecal cells in the ovary. Test article stained tissue elements that were observed in the human but not in the cynomolgus monkey tissues included arachnoid cap cells in cerebellum and spinal cord, ganglion cells in adrenal glands, striated skeletal myocytes in the eye, intrinsic smooth myocytes in esophagus, stomach, and prostate, islet cells in pancreas, luteal cells in ovary and spermatogenic cells in testis (study No 20023264).

2.3.5. Ecotoxicity/environmental risk assessment

Tisotumab vedotin is an antibody-drug conjugate composed of an antibody attached to the cytotoxic payload monomethy auristatin E (MMAE). The determination of the log Dow of the MMAE moiety led to the conclusion that MMAE is not considered a PBT substance.

The applicant refined PEC_{SW} by refining F_{PEN} with data on posology and 5-year prevalence, which resulted in values below the action limit of 0.01 µg/L.

Table 17 Summary of main study results

Substance (INN/Invented Name): **Tisotumab vedotin**				
CAS-number (if available): 1418731-10-8				
PBT screening		Result		**Conclusion**
Bioaccumulation potential- log K_{ow}/D_{ow} For monomethyl auristatin A moiety of vedotin	OECD107	-0.01 at pH 5 1.45 at pH 7 2.23 at pH 9		Potential PBT: N
Phase I				
Calculation	**Value**		**Unit**	**Conclusion**
PEC_{sw}, default	0.019		µg/L	≥ 0.01 threshold: Y
PEC_{sw}, refined (based on posology)	0.0014		µg/L	≥ 0.01 threshold: N

2.3.6. Discussion on non-clinical aspects

Primary pharmacology

Comparable TF binding characteristics and EC_{50} values were seen for tisotumab and tisotumab vedotin by ELISA and flow cytometry, indicating that vcMMAE conjugation do not affect target binding. A binding affinity of 3.2 nM was measured for tisotumab and similar affinity was expected for tisotumab vedotin even though this was not measured. The assumption on comparable affinity is considered acceptable based on the similarities in binding characteristics. However, it would have been more optimal if affinity and avidity was measured for tisotumab vedotin as well.

Tisotumab and tisotumab vedotin was shown to compete with FVlla and dose-dependently inhibit FVIIa binding of TF, thus inhibiting the downstream TF:FVIIa-dependent signalling, as measured by reduced ERK1/2 phosphorylation and IL-8 production.

Tisotumab-mediated internalisation and co-localisation with the lysosomal marker LAMP1 were demonstrated from 1 h after incubation by flow cytometry and confocal microscopy, respectively. Results from the Fab-TAMRA assay using both tisotumab and tisotumab vedotin confirmed that vcMMAE-conjugation did not affect internalisation or intracellular trafficking to the lysosomes (positive signal from 6 h after incubation). Furthermore, this indicated that findings generated by the use of tisotumab as surrogate in the above-mentioned internalisation and lysosomal trafficking studies appears also to be representative for the conjugated form of tisotumab.

Dose-dependent tisotumab vedotin MMAE-mediated cytotoxicity was demonstrated using 26 different TF-expressing tumour cell lines. Overall, results from all 26 TF-expressing tumour cell lines demonstrated that the potency of tisotumab vedotin appeared to be associated with the level of TF expression (i.e. high TF expression -> high potency). However, the effect of tisotumab vedotin cytotoxicity was shown to be reduced by the presence of P-glycoprotein efflux pumps (P-gp). For the cervical cancer cell lines, potent cytotoxicity was observed in two out of three cell lines (IC_{50} of 1.63 and 7.86 nM for cytotoxicity of CaSki and SiHa cells, respectively). Results differed markedly for the ME-108 cell line with an IC_{50} of 575.51 nM. Hence, it was concluded that variation in the direct cytotoxic response can be seen between different cell lines within the same cancer type depending on level of TF-expressions on the plasma membrane but also other factors such as binding and internalisation of the target, sensitivity to the payload, or occurrence of drug efflux pumps.

Bystander cytotoxicity mediated by MMAE was demonstrated as cell death in cells with low TF-expression (TF-low cell) co-cultured with cells with high TF-expression (TF-high cells) exposed to tisotumab vedotin but not in monoculture of TF-low cells.

The ability of tisotumab vedotin and free MMAE to induce immunogenic cell death (ICD) was shown *in vitro* and *in vivo* in a xenograft mouse model by changes in hallmarks of ICD and upregulation immune-modulating genes, respectively.

Studies on Fc-related immunological effect mechanisms indicated that tisotumab and tisotumab vedotin was capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP) but not complement-dependent cytotoxicity (CDC). The immunological effector function was presumable mediated through Fc gamma receptor activation; however, no studies were submitted to confirm this.

The *in vivo* anti-tumour effect of tisotumab vedotin was assessed in several CDX and PDX xenograft models. Only xenograft models relevant for the current indication of cervical cancer has been assessed here (i.e. six cervical cancer PDX model), remaining CDX and PDX models are considered supportive. In general, tisotumab vedotin responding xenograft models appeared to have higher TF expression levels (H-scores) than non-responding models, although anti-tumour activity was also observed in some xenograft models with low TF expression. This finding correlated with above mentioned *in vitro* findings. For the cervical cancer PDX models, a positive effect of tisotumab vedotin was noted in 5 out of 6 models, primarily at dose of 2-4 mg/kg. It should be noted that TF expression was only determined for one out of six cervical cancer PDX models and it is therefore unclear how the level of TF expression has affected the results in these models. No effect of tisotumab vedotin were seen in the CV2320 (cervical carcinoma) PDX model (GMB1015-210). Nevertheless, a small effect appeared to be seen in the CV2320 model when tisotumab vedotin is used in combination with bevacizumab compared to monotreatment with bevacizumab or tisotumab vedotin alone. It is agreed that co-administration could induce changes, such

as e.g. alterations in the tumour microenvironment (TME), possibly potentiating the efficacy of one or both therapeutic agents.

In studies examining the effect of combination treatment, only a small effect of tisotumab vedotin on tumour reduction compared to single agent treatment were shown in combination with bevacizumab (i.e. anti-angiogenic AB-based therapy) or chemotherapy (i.e. cisplatin or carboplatin) in the cervical cancer PDX models (CV1248, CV2320 and CV1802). More interestingly, a tendency towards a more significant effect on prolonged reduction in tumour size or progression free survival was noted. However, evaluation of the later time points and hence conclusions on progression free survival were compromised, especially for the bevacizumab studies, due to differences in dosing schedules in the CV1248 model and lack of sampling points beyond day 25 for the single agents in the CV1802 model.

Taken together, the anti-tumour effector mechanisms mediated by tisotumab vedotinhas been sufficiently demonstrated *in vitro* and *in vivo*. These mechanisms of actions are also reflected in section 5.1 of the SmPC.

Intra-tumoral haemorrhage was observe in one CDX lung cancer model. Further investigations concluded that high doses of unconjugated tisotumab could lead to bleeding due to interference with TF-mediated coagulation, however, the bleeding observed in the CDX lung adenocarcinoma model were most likely a result of the particular tumour morphology even though a potential role of MMAE in enhancing bleeding frequency could not be excluded.

Secondary pharmacology

The effect of tisotumab vedotin and the risk of bleeding were specifically addressed in the secondary pharmacology section using different coagulation assays including a FXa generation assay, a clotting assay, a standard PT assay, a thromboelastography (TEG®) assay and a thrombin generation assay (TGA). In most of these *in vitro* assays tisotumab was used as a surrogate for tisotumab vedotin. This is considered acceptable as both tisotumab and tisotumab vedotin were shown to bind to TF and inhibited binding of FVIIa to TF with similar IC_{50} values, as seen in the primary PD section.

Overall, *in vitro* results showed that tisotumab interfered with TF-induced coagulation through inhibiting FXa (19% inhibition), prolonging clotting time (2.3-fold and 1.4 to 2.6-fold in the clotting assay and TEG analysis, respectively), and reducing thrombin generation. Hence, a risk of bleeding cannot be excluded *in vivo*. Although bleeding was not observed in repeat-dose studies in cynomolgus monkeys, it should still be monitored in the clinical setting and clear information about the risk are provided in the SmPC section 4.4.

Furthermore, potential other targets of tisotumab vedotin-related secondary pharmacology were discussed based on a review of literature identifying PAR-signalling, embryonic development and ocular tissues as areas of concern. This review approach is sufficient when considered in connection with the results of the toxicity studies and the clinical results. Additionally, a tissue cross-reactivity study indicating potential targets of secondary pharmacology was also included and assessed in the toxicology part.

Safety pharmacology

The effect of MMAE on hERG K+ channels were evaluated in a GLP-compliant study. At a concentration of 71.8 µg/mL, approximately 12000-fold higher than the clinically observed C_{max}, a significant different fractional block was noted and the IC_{50} was concluded to be > 71.8 µg/mL. Hence, it is considered unlikely that MMAE would block hERG K+ channels at clinically relevant doses of tisotumab vedotin.

No tisotumab vedotin-related abnormalities in the cardiovascular, respiratory or central nervous system were seen following administration to cynomolgus monkeys in the GLP-compliant repeat-dose toxicity studies (CRL522531).

Pharmacokinetics

Analytical methods

Although method validation studies to support bioanalysis/toxicokinetics of tisotumab, tisotumab vedotin and MMAE in the pivotal toxicology studies were not necessarily GLP compliant they were considered adequately validated and fit-for-purpose.

Absorption

In cynomolgus monkeys, exposure to tisotumab vedotin, defined by C_{max} and AUC, was approximately dose-proportional from 1 mg/kg to 5 mg/kg in males and females. Mean half-life ranged from 24 to 50 hours and no substantial systemic accumulation was found for tisotumab vedotin. No comparison following repeat dosing could be made as the majority of animals developed anti-drug antibodies (ADA) after repeated dosing. ADA positive animals showed a slight decrease in exposure following multiple dose administrations. However, in general, tisotumab vedotin exposures were sufficiently maintained during the treatment period even in the presence of ADA.

After tisotumab vedotin dosing to cynomolgus monkeys for 13 weeks systemic exposure (based on AUC) to free MMAE was generally dose-proportional to dose on Day 1 in males and females up to 5 mg/kg. Exposures to free MMAE were generally comparable between sexes across dose groups. Systemic exposure to free MMAE was up to 10^5-fold lower than systemic exposure to tisotumab vedotin. In some animals that had high ADA titers, a decrease in tisotumab vedotin and an increase in free MMAE in circulation was observed upon subsequent dose administrations.

In cynomolgus monkeys after repeated tisotumab administration, there was little difference in systemic exposure on Day 1 and 85 between sexes. There was no evidence of accumulation of tisotumab. Anti-drug antibody response to tisotumab were limited to 2/10 animals.

Distribution

Findings from the distribution studies with ^{89}Zr-tisotumab vedotin and/or ^{89}Zr-tisotumab and ^{3}H-MMAE partly correlated with skin, bone marrow, eye and male reproductive organs being the target organs of tisotumab vedotin in the toxicology studies in cynomolgus monkeys. It should be noted, that distribution to the eye with lack of elimination were seen for ^{3}H-MMAE but was not estimated for ^{89}Zr-tisotumab vedotin or ^{89}Zr-tisotumab. This finding is notable, taken the clinical adverse eye effects into consideration. ^{89}Zr-tisotumab and ^{3}H-MMAE distributed to the brain, however, at low levels.

Monomethyl auristatin E crosses the placenta and was measurable in foetal serum. No study on excretion to milk has been submitted, however, the lack of data is sufficiently reflected in the SmPC section 4.6. It is unknown whether tisotumab vedotin is excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with Tivdak and for at least 3 weeks after the last dose (see sections 4.6 and 5.3 of the SmPC).

Metabolism

As tisotumab is expected to be catabolised into individual amino acids *in vivo* no traditional metabolism studies were performed for the antibody component of tisotumab vedotin. No disproportionate drug metabolites of MMAE were identified and the metabolism of MMAE was similar in rat, cynomolgus monkey and human hepatocytes. Tisotumab vedotin shares the same linker-drug conjugation of the marketed

product Adcetris (brentuximab vedotin). Metabolite C8 was found to be approximately as cytotoxic and metabolites C4 and C7 less cytotoxic than MMAE in CD30-positive cell lines (Adcetris EPAR, EMA/702390/2012).

An *in vivo* urine and faeces metabolite profiling study in rats with ^{3}H-MMAE provided only limited information. No dedicated *in vivo* studies were conducted to detect metabolites in plasma in neither rats nor cynomolgus monkeys.

Overall, the metabolism of tisotumab vedotin was sufficiently explored.

Excretion

The major route of excretion in rats was via feces (96.7 to 101.8 %), with urinary excretion accounting for <15% of the dose. Unchanged ^{3}H-MMAE was the predominant component in both urine and feces. Excretion was only assessed for MMAE, which is considered acceptable in accordance with ICH S6(R1) guideline, as antibodies are degraded in the body. It should be noted that results from the brentuximab vedotin excretion study, indicated that antibody ^{3}H-MMAE conjugation lowers the rate of excretion and prolong excretion time, as reflected in a significantly longer half-life. Hence, this could potentially also apply for tisotumab vedotin.

Pharmacokinetic drug interactions

Pharmacokinetic drug interactions were investigated in a series of *in vitro* studies to identify the potential of MMAE to act as a substrate, to induce or to inhibit a range of CYP enzymes and drug transporters. *In vitro* MMAE was found to be a quasi-irreversible, mechanism-based CYP3A4/5 inhibitor. Based the low MMAE serum C_{max} in humans (8.23 nM or 5.91 ng/mL) and much higher kinetic interaction coefficient (1.12 µM), MMAE is not expected to alter the pharmacokinetics of other CYP3A4/5 substrate drugs markedly. MMAE was a substrate of P-glycoprotein.

Toxicology

Cynomolgus monkey was selected as the relevant species for non-clinical toxicology studies since tisotumab and tisotumab vedotin binds to human, chimpanzee and cynomolgus tissue factor, but not to other species evaluated including dog, pig, rabbit, rat or mouse as demonstrated in a tissue cross-reactivety study. The apparent affinity of tisotumab vedotin for cynomolgus monkey tissue factor was comparable with that for human tissue factor. For supportive evaluations of MMAE toxicity, rat and cynomolgus monkey were selected as relevant species. In addition, no disproportionate drug metabolites of MMAE were identified and the metabolism of MMAE was similar in rat, cynomolgus monkey and human hepatocytes.

Single-dose toxicity

Single i.v. dose toxicity studies were performed in rats and cynomolgus monkeys with MMAE. All findings were similar to those observed in the repeat-dose studies and included changes in clinical observations, body weights, bone marrow suppression (neutropenia), peripheral blood cell changes, thymic atrophy, gastrointestinal tract and liver toxicity.

Repeat-dose toxicity

In the GLP compliant 13-week repeat-dose study in cynomolgus monkeys the unconjugated antibody tisotumab was well tolerated at doses up to 25 mg/kg. Glassy appearance of the fundus and prolonged prothrombin time (PT) appeared to have little clinical relevance as these changes appeared at doses >40-fold the exposure (based on AUC) at the recommended clinical dose.

Primary tisotumab vedotin-related target organs identified in the repeat-dose toxicity studies showed full reversibility before the next dose administration and the severity, incidence and duration of the reactions decreased with repeated administration. Skin findings (Ulcerative dermatitis, mixed subepidermal inflammatory cell infiltration, epidermal hydropic degeneration/hyperplasia and haemorrhage (subcutis) were attributed to tisotumab vedotin, as administration of tisotumab or MMAE alone did not show adverse effects on skin in rats and/or cynomolgus monkeys. Tissue cross-reactivity studies in humans and cynomolgus monkeys showed tisotumab vedotin-specific staining in the squamous epithelium of the skin, suggesting that these findings in monkeys may be driven by tisotumab vedotin binding to tissue factor in the dermal tissue. Additionally, radiolabeled tisotumab was detected in the skin in a biodistribution study in cynomolgus monkey.

Effects on bone marrow were observed in cynomolgus monkeys administered tisotumab vedotin. Similar effects on bone marrow were observed when MMAE was directly administered to rats and cynomolgus monkeys indicating that MMAE plays a major role in this toxicity. Clinically, anaemia is a potential risk for tisotumab vedotin. Other haematological effects included decreases in total leukocyte and neutrophil counts that were generally reversible. Other findings associated with MMAE treatment included reversible lymphoid depletion in thymus and spleen. Clinically, neutropenia is a potential risk for tisotumab vedotin. Bone marrow, lymphoid and haematology findings in cynomolgus monkeys (3 mg/kg) occurred at systemic exposure levels (based on AUC) 2-fold higher than those at the recommended clinical dose. Haematological effects have been reported with other valine-citrulline-MMAE antibody-drug conjugates (vc-MMAE ADC).

In the 13-week toxicity study, the majority of animals given 5 mg/kg (corresponding to 4-fold the human systemic exposure (based on AUC)) tisotumab vedotin had clinical observations that included reddened eye(s), reddened or swollen conjunctiva (with or without discharge), swollen upper eyelid, partially closed eye, swelling to eyelid with discharge, and/or conjunctivitis. In addition, tissue cross-reactivity studies in humans and cynomolgus monkeys showed tisotumab vedotin-specific staining in ocular tissues, including the conjunctiva. These data suggest that the findings in monkeys are likely driven by tisotumab vedotin binding to tissue factor in the conjunctiva. As the effect in monkeys is dose-related and reversible upon discontinuation of dosing, it is concluded that the findings are likely drug-related but manageable. Section 5.3 of the SmPC includes skin, bone marrow and ocular changes from the repeat-dose studies with clinical relevance.

Testicular toxicity following administration of tisotumab vedotin to sexually mature cynomolgus monkeys consisted of seminiferous tubular atrophy in the testes and absence of sperm, decreased sperm content and epithelial vacuolation in the epididymides. The changes were associated with decreased testicular size, reduced or total absence of sperm counts and sperm motility observed at doses of 1, 3 or 5 mg/kg (corresponding to 0.5- to 4-fold the human systemic exposure (based on AUC)) at the clinically recommended dose). Partial recovery of the findings in testes and epididymides were noted at doses of 3 and 5 mg/kg after a 6-week recovery period. The changes are adequately reflected in the SmPC. Male reproductive changes have been reported with other vc-MMAE ADCs (brentuximab vedotin and enfortumab vedotin) and repeated doses of MMAE at 0.194 mg/kg to sexually mature rats also induced testicular toxicity (study No 7646-118).

Reversible ovarian effects were seen in the study with non-binding control ADC h00-1006(4) (study No 163.66), but no effects were seen in female monkeys treated with tisotumab vedotin in the definitive 13-week repeat dose toxicity study (study No 522531). In study No 163.66, it was noted that the animals were aged between two to three years at initiation of dosing, whereas female cynomolgus monkeys typically reach sexual maturity at four years of age. A potential class effect on the ovaries was mentioned, but no adequate literature discussion was provided to support this statement. The applicant referred to a publication (Neff-LaFord et al., 2024 with authors affiliated to Seagen) in which the non-clinical safety

profiles across 14 vedotin ADCs were compared. The publication indicates that this finding is antigen-independent and can be linked to the mode of action of MMAE on fast dividing cells. This is acknowledged. No discussion was provided as to why there were no similar findings with tisotumab vedotin. The publication indicates that the age of the monkeys could be a contributing factor (older monkeys are less sensitive), however it should be noted that for tisotumab vedotin both young and older monkeys were used, and no effects on the ovaries were observed. Although a discussion on the lack of ovarian findings with tisotumab vedotin,it is agreed that based on all available data that reversible decreases in secondary and tertiary ovarian follicles can be considered as a potential class effect of MMAE-conjugated ADCs, and has been included in SmPC section 5.3. A statement in the fertility subsection of SmPC 4.6 is also included.

Tisotumab vedotin targets tissue factor which is involved in or associated with multiple processes in normal physiology and disease including coagulation. From the data provided no toxicologically meaningful bleeding issues were observed in cynomolgus monkey treated with tisotumab vedotin at clinically relevant doses. Even though, tisotumab vedotin was not associated with any alterations in coagulation in monkeys, patients should be monitored for bleeding events as appropriate and indicated in the SmPC.

In the rat and cynomolgus monkey repeat-dose studies with tisotumab vedotin and MMAE no clinical signs or histopathological findings of peripheral neuropathy were reported. However, in clinical studies with MMAE-ADCs including tisotumab vedotin, peripheral neuropathy has been identified as a risk and included in the RMP.

Genotoxicity

Genotoxicity studies used MMAE rather than tisotumab vedotin and were adequately carried out in accordance with the ICH guideline S2(R1). Monomethyl auristatin E was positive for genotoxicity in the *in vivo* rat bone marrow micronucleus study through an aneugenic mechanism. The genotoxcity of MMAE is adequately reflected in section 5.3 of the SmPC. With regard to the potential genotoxicity of the linker molecule there was sufficient clinical experience from its use in similar products on the market.

Carcinogenicity

The lack of carcinogenicity studies was acceptable based on the proposed indication being in scope of ICH guideline S9.

Developmental and reproductive toxicology

In accordance with ICH guideline S9 dedicated fertility and early embryonic development studies were not conducted. However, testicular and ovarian toxicity was evaluated in the repeat-dose studies.

A GLP-compliant embryo-foetal development study was conducted with MMAE but not with tisotumab vedotin. Administration of 0.2 mg/kg MMAE to rats resulted in adverse embryo-foetal toxicities: Increases in total resorptions, post-implantation loss, early delivery, loss of viable foetuses and foetal external malformations. The findings were consistent with MMAE's disruption of microtubules on rapidly dividing cells during embryogenesis. Tisotumab vedotin can therefore cause foetal harm when administered to a pregnant woman, including embryo foetal toxicity and structural malformations. The pregnancy status of women of childbearing potential should be verified prior to initiating TV treatment. Women of reproductive potential should be advised to use effective contraception during treatment with TV and for 2 months after the last dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of TV. TV should not be used during pregnancy unless the clinical condition of the woman requires treatment with tisotumab vedotin (see sections 4.4, 4.6 and 5.3 of the SmPC).

In accordance with ICH guideline S9 no prenatal and postnatal development studies were conducted.

No juvenile studies were submitted which is accepted, as the proposed marketing authorisation application of tisotumab vedotin is for treatment of adult patients.

Interspecies comparison and exposure margins to clinical exposure

Following multiple dosing with tisotumab vedotin to cynomolgus monkeys 0.5- to 4-fold exposure margins over the predicted adult human exposure were observed. Very low exposure ratios (>100-fold lower in animals compared to humans) were seen when comparing systemic exposure of MMAE of rat and monkey to human. Considering the sought indication low margins of exposure are acceptable and within the scope of the ICH guideline S9. Interspecies comparison data of MMAE was presented by comparing clinical pathology and histopathology data from rats and monkeys after MMAE treatment. Although not included interspecies comparison of MMAE exposure between rats monkeys and humans would have been preferred.

Other toxicity studies

Most monkeys developed ADAs following repeated doses of tisotumab vedotin. However, in the 13-week study tisotumab vedotin exposures were sufficiently maintained during the treatment period despite ADA formation. In some animals with high ADA titers, a decrease in tisotumab vedotin and an increase in free MMAE in circulation was observed upon subsequent dose administrations. Following repeated administration of tisotumab ADA formation was observed in two monkeys in the 13-week study.

The immunotoxic potential of tisotumab, tisotumab vedotin and MMAE was considered minimal based on immunotoxicity evaluations incorporated in the repeat-dose toxicity studies consistent with the ICH guideline S9.

The dependence potential of tisotumab vedotin is unlikely as target is not expressed in the CNS and no effect was observed in CNS safety pharmacology parameters.

No disproportionate drug metabolites of MMAE were identified. Overall, the metabolism of tisotumab vedotin was sufficiently explored.

The pivotal non-clinical GLP-compliant studies used test material that was comparable or identical to the material used in clinical studies and to the intended marketed product. No concern regarding impurities was identified in the Quality Assessment Report. Hence, additional studies on impurities are not warranted.

Monomethyl auristatin E and valine-citrulline-MMAE were adequately evaluated for potential phototoxicity risks. None of the compounds had absorbances in the range of natural sunlight that exceeded the defined threshold for potential phototoxic concern.

Excipients in tisotumab vedotin drug product are well known and are of compendial grade quality.

A tissue cross-reactivity study was conducted with tisotumab vedotin and tisotumab in human and cynomolgus monkey tissues. The staining observed was generally consistent with reported sites of tissue factor expression and was generally observed both on the cell membrane and in the cytosol. Besides minor deviations staining patterns were generally similar between the human and cynomolgus monkey tissue. Tisotumab vedotin stained skin and conjunctiva suggesting that tissue factor-targeting by the conjugated antibody may play a role in toxicity findings in these tissues.

Environmental risk assessment

The applicant performed an initial PBT screening. Based on the determined octanol-water partition coefficients, further PBT/vPvB assessment of MMAE was not warrented. Since the Log Dow at pH 7 was below the trigger value of 3, a bioaccumulation study was not warrented as well.

PEC_{SW} was refined by refining F_{PEN} with data on posology and 5-year prevalence.

Tivdak is not a PBT substance. Considering the ERA data, tisotumab vedotin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

An adequate non-clinical *in vitro* and *in vivo* pharmacology program has been conducted for tisotumab vedotin.

Overall, the non-clinical data package evaluating the pharmacology and toxicity is considered

adequate to support the marketing authorisation.

Tivdak is not a PBT substance. Considering the ERA data, tisotumab vedotin is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 18: List of clinical studies characterizing the pharmacology, safety and efficacy of tisotumab vedotin

Study ID/Study name/Phase/N/Status	Description	Indications	Dosage and Frequency	Data Cutoff Date
GEN701 Phase 1/2 N=195 (27+168) Completed	First-in-human, dose-escalating, open-label, multicenter safety trial of tisotumab vedotin in a mixed population of subjects with solid tumors known to express TF and where the use of systemically administered tubulin inhibitors is part of standard of care. The trial consists of 2 parts: a dose escalation followed by a cohort expansion	Cancer of the ovary, cervix, endometrium, bladder, castration-resistant prostate cancer, esophagus, non-small cell lung cancer and squamous cell carcinoma of the head and neck	Dose Escalation: 0.3 to 2.2 mg/kg Cohort Expansion: 2.0 mg/kg Q3W	Dose Escalation: 31-Jul-2019 Cohort Expansion: 22-Jan-2020
GEN702 Phase 1/2 N=33 (9+24) Completed	Dose-escalating, open-label, multicenter safety trial of tisotumab vedotin in a mixed population of subjects with solid tumors known to express TF and where the use of systemically administered tubulin inhibitors is part of SoC. Dose escalation part followed by a cohort expansion	Ovary, cervix, endometrium, bladder, castration-resistant prostate cancer, esophagus, and non-small cell lung cancer [b]	0.9 or 1.2 mg/kg on days 1, 8 and 15 of a 28-day cycle (3Q4W) 2.0 mg/kg Q3W (June 2017)[a]	Dose Escalation: 10-Feb-2017 Cohort Expansion: 13-Dec-2017
GCT1015-06 Phase 1/2 N=23 (6+17) Completed	Single-arm, open-label, phase 1/2 trial of tisotumab vedotin monotherapy in Japanese subjects with advanced solid malignancies	A mixed population of advanced or metastatic solid tumors in the dose escalation part, and subjects with previously treated recurrent or extra-pelvic metastatic cervical cancer who had received 1 to 2 prior systemic therapy regimens in the dose expansion part	Dose Escalation: 1.5 mg/kg to 2.0 g/kg Q3W Dose Expansion: 2.0 mg/kg Q3W	14-Aug-2020
GCT1015-04 Phase 2 N=101 Completed	Open-label, single arm, global trial of tisotumab vedotin in subjects with recurrent or extra-pelvic metastatic cervical cancer who have experienced disease progression on or after receiving a platinum-containing chemotherapy doublet in combination with bevacizumab (if applicable).	Previously treated r/mCC Subjects may have received no more than 2 prior systemic treatment regimens for recurrent or metastatic disease	2.0 mg/kg Q3W	22-Aug-2019 (for PK data and cQT analysis)
SGNTV-001 Phase 2 (Part A) N=89 Part A completed	Open-label, multicenter trial of tisotumab vedotin in subjects with locally advanced or metastatic disease in selected solid tumors	Colorectal cancer, non-small cell lung cancer, exocrine pancreatic adenocarcinoma, and squamous cell carcinoma of the head and neck [b]	2.0 mg/kg Q3W (Part A)	10-Mar-2023
SGNTV-003 Phase 3 N=489 (250+239) Primary analysis completed	Open-label, randomized (1:1), global, phase 3 study of tisotumab vedotin versus investigator's choice of chemotherapy in subjects with r/mCC who have received 1 or 2 prior lines of systemic therapy for their recurrent or metastatic disease.	r/mCC who have received 1 or 2 prior lines of systemic therapy.	2.0 mg/kg Q3W	01-Mar-2023 (for PK data)

a. Dosing regimen changed to 2.0 mg/kg Q3W (June 2017) due to severe ocular toxicity.
b. Subjects have failed available standard treatments or are otherwise not candidates for standard therapy.

Table 19: List of studies using human biomaterials

Study Item	Study No.	Study Content	Human Biomaterial	MMAE Concentration	Position in the eCTD
In vitro protein binding	XS-0025	Plasma protein binding	Plasma	1, 10, and 100 nM	m2.6.4, Section 4.4
RBC distribution	14-0271-GNE-A1	RBC partitioning potential	Blood and plasma	2 to 5000 nM	m2.6.4, Section 4.5
In vitro metabolism	XT084007	Metabolite characterisation	Human hepatocytes	[^{3}H]-MMAE at 10 µM	m2.6.4, Section 5.1
	XT084006	CYP Reaction phenotyping	NADPHfortified human liver microsomes;	[^{3}H] MMAE at 6 and 16 µM	m2.6.4, Section 5.1

Study Item	Study No.	Study Content	Human Biomaterial	MMAE Concentration	Position in the eCTD
			recombinant human CYP enzymes		
In vitro metabolism (interaction)	XT133043	CYP induction	Human hepatocytes	1, 10, 100, 1000 nM	m2.6.4, Section 7.1
	XT085021	CYP inhibition	Human liver microsomes	Range 0.1 to 100 µM	m2.6.4, Section 7.2
In vitro transport (efflux transporter)	XT108004	P-gp/ABCB1 inhibition P-gp/ABCB1-mediated transport	P-gpexpressing- Caco-2 cells	1, 10, 100 µM	m2.6.4, Section 7.3
	RPT-01709	P-gp, BCRP/ABCG2, and MRP2/ABCC2	Caco-2 cell monolayer	1, 10, 100 µM	m2.6.4, Section 7.3
In vitro transport (uptake transporter)	PDM-0008	OATP1B1/SLCO1B1	OATP1B1-expressing CHO or HEK293 cells	10 or 100 nM	m2.6.4, Section 7.3
	PDM-0009	OATP1B3/SLCO1B3	OATP1B3-expressing CHO or HEK293 cells	10 or 100 nM	m2.6.4, Section 7.3
	PDM-0010	OCT2/SLC22A2	OCT2-expressing CHO or HEK293 cells	10 or 100 nM	m2.6.4, Section 7.3
	PDM-0011	OAT1/SLC22A6	OAT1-expressing CHO or HEK293 cells	10 or 100 nM	m2.6.4, Section 7.3
	PDM-0012	OAT3/SLC22A8	OAT3-expressing CHO or HEK293 cells	10 or 100 nM	m2.6.4, Section 7.3
In vitro transport (uptake and efflux transporters)	15-3234	BCRP, BSEP, MRP2, OAT1, OAT3, OATP1B1 OATP1B3, OCT1/, and OCT2	Vesicular transport system/ Transporterexpressing CHO or HEK 293 cells	0.008 to 5 µM	m2.6.4, Section 7.3

ABC=ATP-binding cassette subfamily; BCRP=Breast Cancer Resistance Protein; BSEP=bile salt export pump; CHO=Chinese hamster ovary; CYP=cytochrome P450; eCTD=Electronic Common Technical Document; HEK=human embryonic kidney; MMAE=monomethyl auristatin E; MRP2=Multidrug Resistance Protein2; NADPH=nicotinamide adenine dinucleotide phosphate hydrogen; OAT=organic anion transporter; OATP=organic anion transporting polypeptide; OCT=organic cation transporter; P-gp=P-glycoprotein 1; SLC22A=solute carrier family 22 member; RBC=red blood cell; SLCO=Solute carrier organic anion transporter family member.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

The clinical pharmacology of tisotumab vedotin has been characterised based on data from 6 clinical studies that are listed in Table 22. In GEN701, subjects were given tisotumab vedotin across 8 dose levels ranging from 0.3 to 2.2 mg/kg Q3W during dose escalation and at 2.0 mg/kg Q3W in dose expansion. In GEN702 subjects were given tisotumab vedotin at 0.9 or 1.2 mg/kg on Days 1, 8, and 15 of a 28-day cycle (3 times every 4 weeks [3Q4W]) before the protocol was amended to change the dose to 2.0 mg/kg Q3W for safety reasons. In GCT1015-06, subjects were given tisotumab vedotin at 2 dose levels (1.5 mg/kg and 2.0 mg/kg) in the dose escalation phase and at 2.0 mg/kg by IV infusion Q3W in the dose expansion phase. In studies GCT1015-04 and SGNTV-001, subjects were given tisotumab vedotin at 2.0 mg/kg Q3W. In SGNTV-003, randomised subjects were given tisotumab

vedotin 2.0 mg/kg Q3W or investigator's choice of chemotherapy. None of the studies were standalone PK studies.

Bioanalytical methods

Bioanalytical studies were conducted in different sites, nevertheless the original methods were cross-validated when shifting from one site to another prior to supporting new clinical studies.

PD biomarkers

cTF in plasma was included as a biomarker in study GCT1015-04. As correlation to Best Overall Response was found this biomarker was not included in the Phase 3 study SGNTV-003.

Assays of immunogenicity:

Antidrug Antibody (ADA)

Drug tolerance: At 25 ng/mL ADA, drug tolerance was 100 µg/mL ADC at the three sites studied. All samples for ADA/ATA were taken pre-dose or after end of treatment and C_{trough} was below limit of quantification.

Neutralizing Antibody (NAB)

NAB assay sensitivity 746 ng/mL in study SGNTV-003, cell-based assay, fully validated, in one sites was different in other sites where the sensitivity was of 60 ng/mL (study GCT1015-04, electrochemilumine-scence, qualified).

Evaluation and qualification of models

Population PK analysis and exposure-response analyses were performed using R and NONMEM software. The LAPLACIAN method was used for all model estimations.

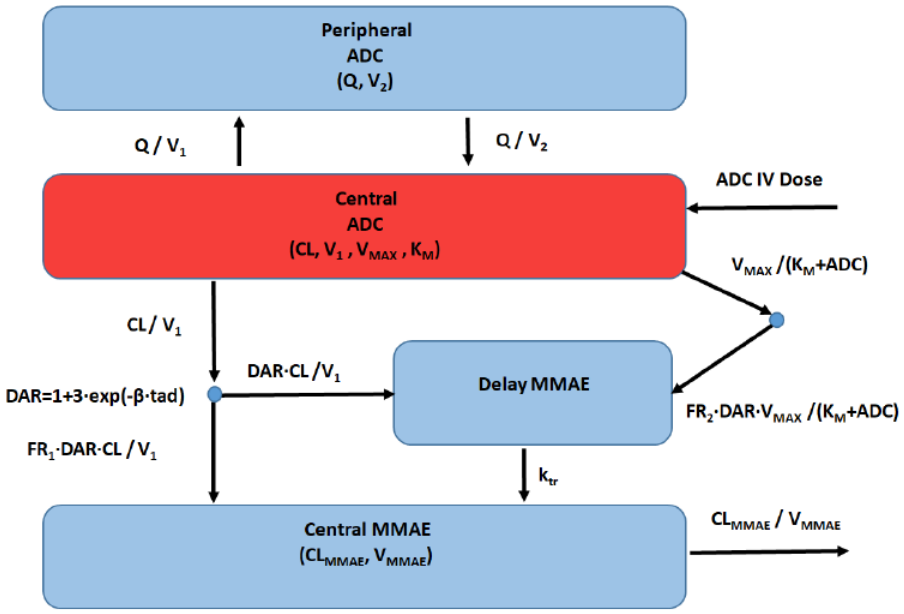
Pop PK modelling

Tisotumab vedotin PK was described by a complex four-compartment Pop PK model consisting of a two-compartment ADC model with parallel linear and Michaelis-Menten elimination, a delay compartment, and a one-compartment MMAE model (Model 137, In-Text Figure 1). The model was developed on an earlier data set from two Phase 1/2 and two Phase 2 studies in subjects with various solid tumours known to express tissue factor, including women with cervical cancer.

Figure 7 Schematic representation of the structural ADC-MMAE model

CL: ADC clearance; Q: ADC inter-compartment clearance; V_1: ADC central volume; V_2: ADC peripheral volume; V_{max}: maximum ADC Michaelis-Menten elimination rate; K_M: Michaelis-Menten constant of ADC elimination.

CL_{MMAE}: MMAE apparent clearance; V_{MMAE}: MMAE apparent central volume. FR_1: fraction of ADC non-specific elimination that goes to the central compartment; FR_2: fraction of ADC target-mediated elimination that goes to the delay compartment; k_{tr}: delay compartment rate constant; DAR: drug to antibody ratio assumed to follow an exponential decay from the initial value of 4 to the lowest value of 1; β: rate constant of DAR decline with time after dose; tad: time after dose.



The model included effects of covariates: body weight, sex and baseline albumin (ADC); body weight, baseline albumin, baseline tumour size, cancer type, ECOG, eGFR, hepatic impairment and age (MMAE). Body weight had most impact on ADC exposure. Despite a weight proportional dosing, exposure increased with body weight.

Final parameter estimates of Model 137 are displayed in Table 23,Table 24,Table 25.

Table 20 Estimates of structural fixed-effect parameters, final ADC-MMAE Model 137

Parameter		Description	Value	RSE%	95% CI
ADC parameters					
CL (L/day)	θ_1	non-specific clearance	1.42	5.19	1.28 ; 1.57
Q (L/day)	θ_2	inter-compartment clearance	4.01	2.93	3.78 ; 4.24
V_1 (L)	θ_3	central volume	3.10	1.23	3.03 ; 3.18
V_2 (L)	θ_4	peripheral volume	4.47	2.3	4.27 ; 4.68
V_{max} (µg/mL/day)	θ_5	maximum MM elimination	3.35	11.7	2.58 ; 4.12
K_M (µg/mL)	θ_6	MM constant	3.44	12.3	2.61 ; 4.27
σ_{prop}	θ_7	SD of ADC residual error: proportional part	0.129	2.07	0.124 ; 0.134
σ_{add} (µg/mL)	θ_8	SD of ADC residual error: additive part	0.0173	7.66	0.0147 ; 0.0199
$t_{1/2,\alpha}$ (day)		ADC distribution half-life	0.28	Derived from CL, V_1, V_2, and Q	
$t_{1/2,term}$ (day)		ADC terminal half-life	4.19		
MMAE parameters					
k_{tr} (1/day)	θ_9	Rate constant of delay	0.271	1.35	0.264 ; 0.278
CL_{MMAE} (L/day)	θ_{10}	MMAE Clearance	42.8	7.4	36.6 ; 49.0
V_{MMAE} (L)	θ_{11}	MMAE central volume	2.09	9.82	1.69 ; 2.50
β_{DAR} (1/day)	θ_{12}	Rate constant of DAR decay	0.0189	26.5	0.0091 ; 0.0288
σ_{prop}	θ_{13}	SD of MMAE residual error: proportional part	0.282	2.13	0.27 ; 0.294
σ_{add} (ug/mL)	θ_{14}	SD of MMAE residual error: additive part	0.0113	4.42	0.0103 ; 0.0123
FR_1	θ_{15}	Fraction of MMAE non-specific elimination to central compartment	0.0205	7.94	0.0173 ; 0.0237
FR_2	θ_{16}	Fraction of MMAE target-mediated elimination to delay compartment	0.0508	27.7	0.0232 ; 0.0784
$t_{1/2,KTR}$ (day)		MMAE delay half-life	2.56	$t_{1/2,KTR} = \log(2)/k_{tr}$	
$t_{1/2,MMAE}$ (day)		MMAE terminal half-life	0.0339	$t_{1/2,KTR} = \log(2)/K_{MMAE}$; $K_{MMAE} = CL_{MMAE}/V_{MMAE}$	

SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100·abs(SE/PE); 95% CI: 95% confidence interval Source: 137ParEst.csv (DiagnosticPlotsCombined.R, Covariate_Exposure_Plot.R)

Table 21 Estimates of Covariate Fixed-Effect Parameters, Final ADC-MMAE Model 137

Parameter		Description	Value	RSE%	95% CI
$CL_{WT} = Q_{WT}$	θ_{17}	Weight effect on CL, Q	0.495	9.86	0.399 ; 0.591
$V_{1,WT}$	θ_{18}	Weight effect on V_1	0.380	12.1	0.29 ; 0.47
$V_{2,WT}$	θ_{19}	Weight effect on V_2	0.622	7.9	0.526 ; 0.718
CL_{ALB}	θ_{20}	Albumin effect on CL	-0.396	18.9	-0.543 ; -0.25
$V_{1,ALB}$	θ_{21}	Albumin effect on V_1	-0.197	32.1	-0.32 ; -0.0729
CL_{SEXM}	θ_{22}	Male effect on CL	1.09	3.55	1.02 ; 1.17
$V_{1,SEXM}$	θ_{23}	Male effect on V_1	1.13	2.11	1.09 ; 1.18
$CL_{MMAE,WT}$	θ_{24}	Weight effect on CL_{MMAE}	0.457	24.6	0.237 ; 0.677
$V_{MMAE,WT}$	θ_{25}	Weight effect on V_{MMAE}	0.895	13.2	0.663 ; 1.13
$CL_{MMAE,ALB}$	θ_{26}	Albumin effect on CL_{MMAE}	0.935	26.5	0.449 ; 1.42
$CL_{MMAE,Non-Cervical}$	θ_{27}	Non-cervical effect on CL_{MMAE}	1.22	5.99	1.07 ; 1.36
$CL_{MMAE,SUMDIAM}$	θ_{28}	Tumor size effect on CL_{MMAE}	-0.147	20	-0.205 ; -0.0895
$CL_{MMAE,GFR}$	θ_{29}	eGFR effect on CL_{MMAE}	0.271	38.6	0.0659 ; 0.475
$CL_{MMAE,ECOG}$	θ_{30}	ECOG > 0 effect on CL_{MMAE}	0.803	6.59	0.699 ; 0.907
$CL_{MMAE,HEP}$	θ_{31}	Hepatic impairment effect on CL_{MMAE}	0.853	7.98	0.719 ; 0.986
$V_{MMAE,ECOG}$	θ_{32}	ECOG > 0 effect on V_{MMAE}	0.827	6.13	0.727 ; 0.926
$V_{MMAE,ALB}$	θ_{33}	Albumin effect on V_{MMAE}	0.575	41.6	0.106 ; 1.04
$k_{tr,AGE}$	θ_{34}	Age effect on k_{tr}	-0.252	15.3	-0.327 ; -0.176
$k_{tr,WT}$	θ_{35}	Weight effect on k_{tr}	-0.175	24.3	-0.258 ; -0.0916
σ_{702}	θ_{36}	Study 702 effect on ADC residual error	1.42	5.79	1.26 ; 1.58

SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100·abs(SE/PE); 95% CI: 95% confidence interval. Source: 137ParEst.csv (DiagnosticPlotsCombined.R)

Table 22 Estimates of Variance Parameters, ADC-MMAE Model 137

Parameter		Value	RSE%	95% CI	CV	Shrinkage
ADC parameters						
ω^2_{CL}	Ω_{11}	0.0538	11.0	0.0422 ; 0.0654	CV=23.2%	3.6%
R $\omega_{CL}\omega_{V1}$	Ω_{12}	0.0166	14.0	0.012 ; 0.0211	R=0.415	
ω^2_{V1}	Ω_{22}	0.0296	8.59	0.0246 ; 0.0346	CV=17.2%	4.3%
R $\omega_{V1}\omega_{V2}$	Ω_{23}	0.0145	14.8	0.0103 ; 0.0187	R=0.586	
ω^2_{V2}	Ω_{33}	0.0208	13.9	0.0151 ; 0.0264	CV=14.4%	19.2%
ω^2_{σ}	Ω_{44}	0.0561	12.7	0.0422 ; 0.0701	CV=23.7%	24.6%
σ^2	Σ_{11}	1	fixed			7.9%
MMAE parameters						
ω^2_{ktr}	Ω_{55}	0.0212	10.6	0.0168 ; 0.0256	CV=14.5%	15.8%
ω^2_{CLmmae}	Ω_{66}	0.299	7.85	0.253 ; 0.345	CV=54.7%	3.6%
R_{MMAE} $\omega_{CLMMAE}\omega_{VMMAE}$	Ω_{67}	0.125	14.4	0.0901 ; 0.161	R=0.495	
ω^2_{VMMAE}	Ω_{77}	0.215	9.77	0.174 ; 0.256	CV=46.3%	8.0%
ω^2_{σ}	Ω_{88}	0.0712	10.6	0.0564 ; 0.0861	CV=26.7%	16.1%
σ^2	Σ_{22}	1	fixed			5.2%

ω^2 and σ^2: variances of inter-individual and residual variability, respectively, R: correlation coefficient, SE: Standard Error; PE: Parameter Estimate; RSE (%): Relative Standard Error = 100·abs(SE/PE); 95% CI: 95% confidence interval, CV: coefficient of variation

The model parameters were estimated with good precision for ADC (RSE% range: 1.23-12.3) and with less precision for MMAE (RSE% range: 1.35-27.7). The model was evaluated by GoF plots, NPDE plots, VPCs and pcVPCs based on 500 simulations.

The final model (Model 137) was used to describe the exposure data from Phase 2 Study GCT1015-06 in Japanese subjects with solid tumours (n=23) and from the Phase 3 Study SGNTV-003 in women with cervical cancer (n=230) by external validation (denoted Model 300).

Absorption

Tisotumab is by definition fully absorbed into circulation as it administered by intravenous infusion. Bioavailability of tisotumab vedotin is by definition 100% as it administered by venous infusion.

Bioequivalence

During development, there were no changes to the formulation. However, the drug product manufacturing process was scaled up from Scale I to Scale II, then to Scale III to meet the requirements of clinical and commercial manufacturing. The changes from manufacturing process Scale I to Scale II are summarised in the quality section.

Clinical studies GEN701, GEN702 used Scale I, GCT1015-06 used scale II, GCT1015-04, SGNTV-001 and SGNTV-003 used both scale II and III.

Any effects of scale on pharmacokinetic parameters were evaluated using the POPPK model, see Figure 20.

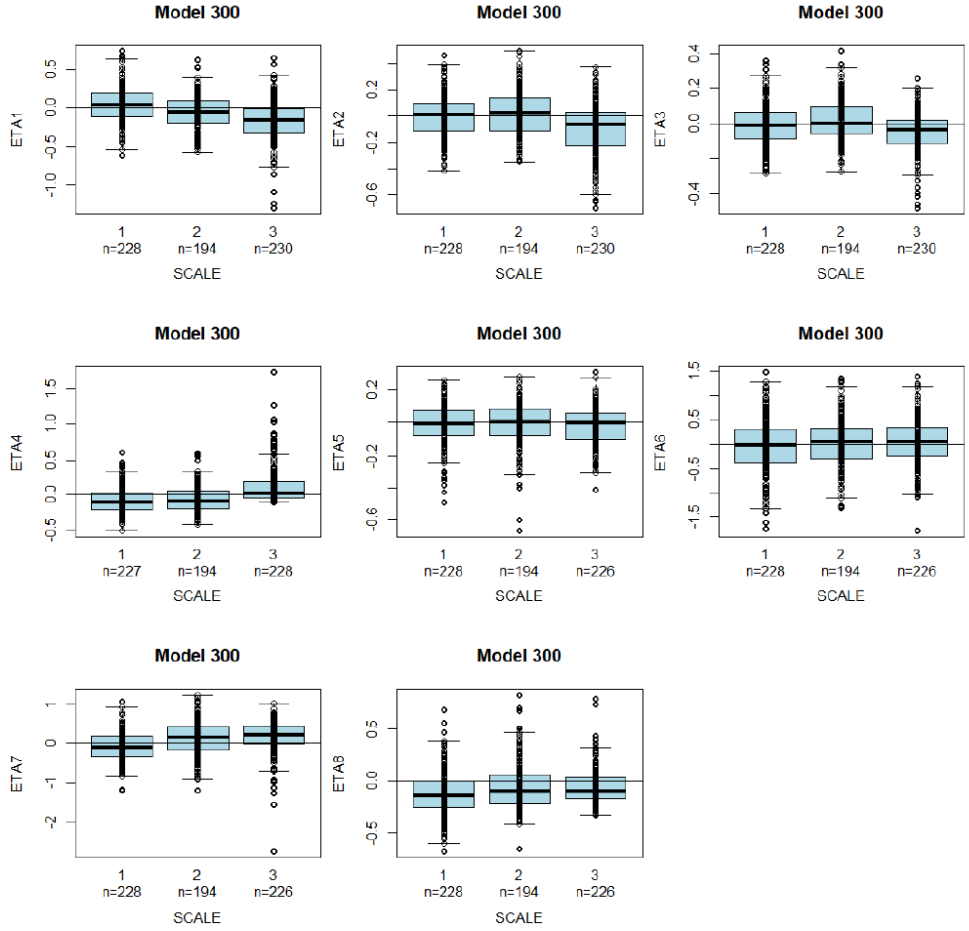


Figure 8 Relationships between interindividual random effects and administered drug product were evaluated using the POPPK model 300.

The individual random effects are plotted versus material scale using box and whisker plots. Median values of the random effects are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Solid lines at y = 0 are included for reference. ETA1: the random effect on CL; ETA2: the random effect on V1; ETA3: the random effect on V2; ETA4: the random effect on the ADC residual error (ERR); ETA5: the random effect on ktr; ETA6: the random effect on CLMMAE; ETA7: the random effect on VMMAE; ETA8: the random effect on the MMAE residual error (ERR); SCALE: drug product.

Distribution

MMAE Plasma Protein Binding

MMAE protein binding in human plasma and RBC partitioning have been evaluated (Study XS 0025 and Study 14 0271 GNE A1). In humans, 67.9% to 82.2% of ^{3}H MMAE was bound to plasma proteins (1100 nM-).

MMAE Distribution to Blood cells

For details on blood to plasma ratio study, refer to Non-clinical section. The cytotoxic payload of tisotumab vedotin, MMAE showed species-dependent blood-to-plasma concentration ratios which were 9.47 to 11.8 in mouse, 1.86 to 2.36 in rat, 1.40 to 1.57 in cynomolgus monkey, and 0.926 to 0.976 in

human at 2 and 20 nM (clinically relevant concentrations). These results suggest that MMAE has minimal RBC partitioning in human blood and that RBC partitioning is dependent on species.

MMAE Tissue Distribution

Based on PopPK analysis, following a 2.0 mg/kg tisotumab vedotin IV dose, the typical central volume of distribution was estimated to be 3.10 L and the typical peripheral volume of distribution was estimated to be 4.47 L (PopPK Report SR1015 248). Volume of distribution for TAB was a little lower than for ADC.

Estimates of Volume of distribution of tisotumab vedotin ADC and TAB was calculated from Non-compartmental analysis of bioanalytical data obtained in GEN701, see Tables below.

Table 23. Volume of distribution after NCA analysis (first in human study, GEN701)

Timepoint	0.3 mg/kg (N=3)	0.6 mg/kg (N=3)	0.9 mg/kg (N=3)	1.2 mg/kg (N=3)
Cycle 2				
CL (mL/h/kg)				
n	0	2	3	3
Mean (std)		1.72 (0.086)	1.44 (0.091)	1.08 (0.113)
Geometric Mean (CV %)		1.72 (4.98)	1.44 (6.32)	1.07 (10.45)
Median		1.72	1.45	1.04
Min, Max		1.7, 1.8	1.3, 1.5	1.0, 1.2
Vz (mL/kg)				
n	0	2	3	3
Mean (std)		76.87 (7.325)	69.89 (5.581)	62.69 (3.781)
Geometric Mean (CV %)		76.69 (9.53)	69.74 (7.99)	62.61 (6.03)
Median		76.87	70.45	62.56
Min, Max		71.7, 82.0	64.1, 75.2	59.0, 66.5

Timepoint	1.5 mg/kg (N=3)	1.8 mg/kg (N=3)	2.0 mg/kg (N=3)	2.2 mg/kg (N=6)
Cycle 2				
CL (mL/h/kg)				
n	3	2	2	3
Mean (std)	2.09 (0.562)	0.94 (0.227)	1.31 (0.250)	1.03 (0.117)
Geometric Mean (CV %)	2.05 (26.80)	0.93 (24.03)	1.30 (19.06)	1.03 (11.34)
Median	2.03	0.94	1.31	1.01
Min, Max	1.6, 2.7	0.8, 1.1	1.1, 1.5	0.9, 1.2
Vz (mL/kg)				
n	3	2	2	3
Mean (std)	100.56 (20.937)	73.69 (31.638)	74.85 (3.133)	72.82 (4.213)
Geometric Mean (CV %)	99.20 (20.82)	70.21 (42.93)	74.82 (4.19)	72.74 (5.79)
Median	89.26	73.69	74.85	71.39
Min, Max	87.7, 124.7	51.3, 96.1	72.6, 77.1	69.5, 77.6

AUC0-inf is not calculated where the percentage of the AUC that is due to the extrapolation is more than 20%.

Elimination

A clinical DDI study for another MMAE containing ADC, brentuximab vedotin, is available in literature (Han 2013). Based on that study evaluation of the primary excretion route in an abbreviated design is

not anticipated to reach 100% recovery. The primary excretion route of MMAE was via feces (over a 1 week period, ~24% of total MMAE administered was excreted in feces and urine, of which ~72% was excreted in feces). Sample analysis were performed using LC-MS/MS as MMAE was not radiolabeled

Clearance

Based on PopPK analysis, the typical value of nonspecific linear CL of tisotumab vedotin was 1.42 L/day. Following a tisotumab vedotin dose of 2.0 mg/kg, about 60% of tisotumab vedotin was eliminated by linear CL; the remainder was eliminated through saturable CL pathways. The apparent CL of unconjugated MMAE (CLMMAE) was 42.8 L/day (PopPK Report SR1015 248). Geometric mean CL was calculated by non-compartmental analysis in GEN701 for tisotumab vedotin (ADC) to be in the range of 0.93-2.05 mL/h/kg. Clearance was not calculated for MMAE using non-compartmental analysis. For tesutomab vedotin (ADC), anticipating mean body weight of 70 kg, CL of 0.93 mL/h/kg corresponds to 0.93/1000 mL) *24 hour *70 kg = 1.6 L/Day. CL of 2.05 mL/h/kg corresponds to (2.05/1000 mL) *24 hour*70 kg = 3.4 L/day.

Half life

Based on PopPK analysis, following a 2.0 mg/kg tisotumab vedotin IV dose, ADC elimination exhibited a multi-exponential decline with a median $t_{1/2}$ of 4.04 days.

Based on PopPK analysis, elimination of MMAE appeared to be limited by its rate of release from tisotumab vedotin. The terminal $t_{1/2}$ of MMAE was defined by the delay compartment and estimated to be 2.56 days.

Geometric mean $t_{½}$ of ADC was calculated by non-compartmental analysis in study GEN701 to be in the range of 13.54 - 48.98 hours (0.56 – 2.04 Days) covering the dose range of 0.3 mg/kg to 2.2 mg/kg, i.e. highly dose dependent. Non-linear clearance showed high impact at the lower doses as expected for target mediated drug disposition of a monoclonal antibody. Geometric mean $t_{½}$ for MMAE was in the range of 60.71-78.94 hours (2.5-3.3 days).

Accumulation

Tisotumab vedotin is not accumulating between infusions, when administered every 3 weeks at or below 2 mg/kg.

Metabolism

Metabolism of the antibody part of tisotumab vedotin is believed to be by catabolic proteolytic pathways into smaller peptides and eventually amino acids and is therefore not further evaluated.

MMAE metabolism was evaluated *in vitro* by CYP enzyme phenotyping, induction, and inhibition studies and by characterisations of metabolite structure (studies XT084006, XT084007, XT133043, and XT085021).

In vitro studies in human liver microsomes showed that MMAE undergoes metabolism primarily by CYP3A4. Radio-chromatographic profiles revealed 3 abundant metabolites, corresponding to metabolites C4, C7, and C8 as characterised by mass spectrometry.

A clinical evaluation of the metabolism of MMAE in humans with another MMAE containing ADC, brentuximab vedotin, was performed with the excretion (urine and faeces) samples collected (Han, 2013). MMAE metabolites in urine and faeces were identified by tandem and high-resolution mass spectrometry. MMAE was the only observed species in unconcentrated urine and faeces liquid–liquid extracts. However, after concentrating the liquid–liquid extracts ten-fold, 8 metabolites of MMAE were detected.

Multiple metabolites were identified in urine: an amide hydrolysis product (C5); a hydroxylation product (C6); a demethylation product (C7); and a dehydrogenation product (C8). Metabolites detected in faeces included: a demethylation product (C4), C5, and C8.

Since the same drug linker conjugate is used in both brentuximab vedotin and tisotumab vedotin, the same MMAE metabolic pathways are predicted *in vivo* for tisotumab vedotin.

The metabolism of MMAE was evaluated *in vitro* in hepatocytes from rat, monkey and humans. All human metabolites were also formed in rat and/or monkey hepatocytes.

There is no information of circulating metabolites of MMAE in plasma.

Consequences of possible genetic polymorphism

In Study XT084006, [^{3}H]-MMAE was converted to eight radioactive components by NADPH-fortified human liver microsomes, the major components being 7.0, 8.6 and 11.1 (retention times). These components are proposed metabolites formed by O-demethylation (−14 amu; C4), N-demethylation (−14 amu; C7) and dehydrogenation (−2 amu; C8), respectively. The formation of these major components by human liver microsomes was primarily mediated by CYP3A4 as determined by correlation analysis, experiments with recombinant human CYP enzymes and experiments with CYP-selective inhibitors. Additional CYP enzymes (e.g., CYP2D6) may be minor contributors to the formation of these components, and carbonyl reductases may conceivably contribute to the formation of component 11.1 (C8). Hence, CYP3A4 is by far the most important CYP responsible for metabolising MMAE. Genetic polymorphism of CYP3A4 is very rare.

Dose proportionality and time dependencies

In study GEN701, full pharmacokinetic profiles of tisotumab vedotin (ADC), Tisotumab Antibody (TAB) and MMAE were obtained in patients at dose levels of 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.0 and 2.2 mg/kg, see Table 27, Table 29and Table 32Analysis of dose proportionality was performed using the Power model, see Table 28, Table 27 and Table 34.

Table 24 Summary of Cycle 1 Pharmacokinetic Parameters of tisotumab vedotin: Dose Escalation, Study GEN701

Dose cohort	T_{max} Median (range) (h)	C_{max} – Geometric Mean (CV%) (µg/mL)	AUC_{0t} – Geometric Mean (CV%) (day×µg/mL)
0.3 mg/kg (N=3)	1.07 (0.9, 3.2)	4.78 (12.35)	2.5 (3.1)
0.6 mg/kg (N=3)	1.12 (1.1, 1.4)	12.20 (9.47)	15.4 (8.2)
0.9 mg/kg (N=3)	1.43 (1.2, 1.5)	19.81 (17.32)	25.1 (16.9)
1.2 mg/kg (N=3)	1.23 (1.0, 1.2)	34.67 (18.48)	45.2 (9.3)
1.5 mg/kg (N=3)	1.17 (1.0, 1.2)	23.12 (21.10)	33.1 (19.0)
1.8 mg/kg (N=3)	1.15 (1.0, 1.4)	35.42 (39.20)	63.0 (49.3)
2.0 mg/kg (N=3)	1.22 (1.1, 1.3)	32.30 (22.08)	52.3 (33.1)
2.2 mg/kg (N=6)	1.08 (1.0, 1.4)	55.53 (10.31)	84.9 (33.7)

AUC_{0-t}=area under the concentration-time curve from dosing time (time 0) to time t; C_{max}=maximal concentration; CV=coefficient of variation; T_{max}=time to reach maximum concentration

Table 25 . Analysis of dose proportionality for ADC (Power Model): Study GEN701

Parameter	N	Slope	90% CI
C_{max} (µg/mL)	27	1.1	(0.96,1.25)
AUC_{0-t}(day*µg/mL)	27	1.6	(1.37,1.79)
AUC_{0inf} (day*µg/mL)	23	1.3	(1.03,1.57)

Table 26 Summary of Pharmacokinetic Parameters of TAb: Dose Escalation, Study GEN701

Dose Cohort	T_{max}Median (range) (h)	C_{max} – Geometric Mean (%CV) (µg/mL)	AUC_{0t} – Geometric Mean (%CV) (day×µg/mL)
0.3 mg/kg (N=3)	3.17 (1.1, 3.2)	4.90 (13.00)	2.9 (0.5)
0.6 mg/kg (N=3)	1.12 (1.1, 1.4)	11.84 (8.31)	15.4 (53.1)
0.9 mg/kg (N=3)	1.43 (1.2, 1.5)	17.98 (11.64)	35.0 (18.9)
1.2 mg/kg (N=3)	1.23 (1.0, 1.2)	29.30 (10.14)	60.4 (13.4)
1.5 mg/kg (N=3)	1.17 (1.0, 1.2)	23.55 (25.16)	44.9 (27.8)
1.8 mg/kg (N=3)	1.15 (1.0, 1.4)	30.57 (37.42)	86.7 (54.3)
2.0 mg/kg (N=3)	1.22 (1.1, 1.3)	38.78 (21.77)	85.9 (36.7)
2.2 mg/kg (N=6)	1.08 (1.0, 1.4)	58.02 (12.77)	123.0 (34.7)

AUC_{0-t}=area under the concentration-time curve from dosing time (time 0) to time t; C_{max}=maximal concentration; CV=coefficient of variation; T_{max}=time to reach maximum concentration

Table 27. Analysis of Dose Proportionality for TAb (Power Model): Study GEN701

Parameter	N	Slope	90% CI
C_{max} (µg/mL)	27	1.1	(1.01, 1.26)
AUC_{0-t} (day*µg/mL)	27	1.7	(1.51, 1.98)
AUC_{0inf} (day*µg/mL)	22	1.3	(1.02, 1.66)

Table 28. Summary of Cycle 1 Pharmacokinetic Parameters of MMAE: Dose Escalation, Study GEN701

Dose Cohort	T_{max}Median (range) (h)	C_{max} – Geometric Mean (%CV) (ng/mL)	AUC_{0-t} – Geometric Mean (%CV) (day*ng/mL)
0.3 mg/kg (N=3)	23.33 (23.3, 25.1)	0.760 (62.505)	6.20 (72.05)
0.6 mg/kg (N=3)	25.10 (18.6, 25.3)	1.673 (30.756)	12.61 (28.18)
0.9 mg/kg (N=3)	25.47 (22.3, 25.6)	1.524 (54.491)	12.22 (67.23)
1.2 mg/kg (N=3)	24.78 (22.7, 25.2)	1.410 (19.149)	11.63 (52.69)
1.5 mg/kg (N=3)	25.00 (25.0, 25.3)	2.807 (39.398)	26.55 (44.24)
1.8 mg/kg (N=3)	25.30 (25.1, 171.6)	2.587 (29.172)	22.55 (57.26)
2.0 mg/kg (N=3)	139.35 (25.3, 163.9)	6.351 (61.505)	67.42 (59.98)
2.2 mg/kg (N=6)	152.50 (23.3, 166.9)	4.877 (31.350)	26.47 (59.35)

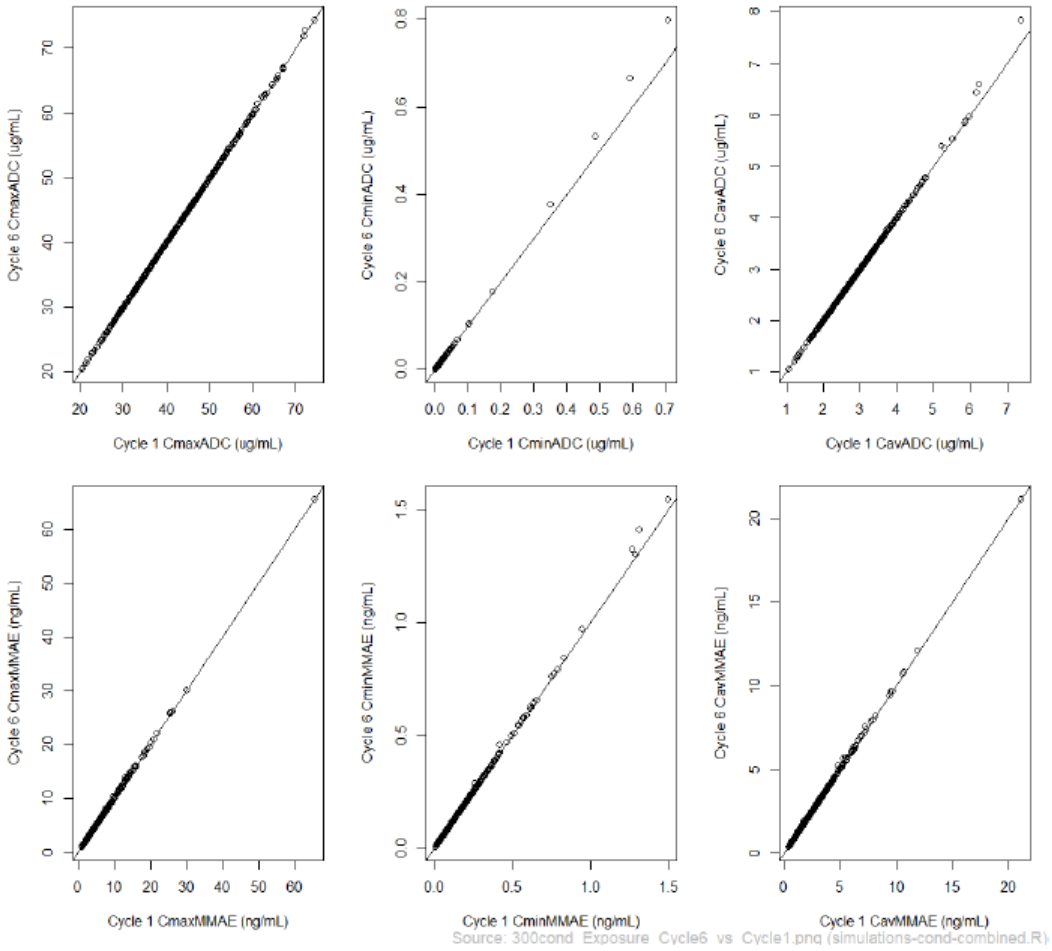
AUC_{0-t}=area under the concentration-time curve from dosing time (time 0) to time t; C_{max}=maximal concentration; CV=coefficient of variation; T_{max}=time to reach maximum concentration

Table 29 Analysis of Dose Proportionality for MMAE (Power Model): Study GEN701

Parameter	N	Slope	90% CI
C_{max}(ng/mL)	27	0.9	(0.66,1.18)
AUC_{0-t}(day*ng/mL)	27	0.9	(0.40,1.31)
AUC_{0-inf}(day*ng/mL)	11	0.7	(0.33,1.11)

PK appears not to be time dependent, see figure below.

Figure 9 Correlation of Exposure Estimates in Cycle 6 versus Cycle 1 following 2 mg/kg Q3W Dosing (POPK SR1015-248)



No time-dependent PK was observed for ADC or TAB in Study?????

The clearance of MMAE was time-dependent for brentuximab vedotin (i.e. increased Clearance with time, Han 2013). However, this was apparently not observed for tisotumab vedutin. No accumulation of ADC or MMAE was observed either.

Therapeutic Window

The Dose Escalation Part applied a standard 3 (+3) design to evaluate tisotumab vedotin at doses ranging from 0.3 to 2.6 mg/kg (0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.2, and 2.6 mg/kg). On the 2.2 mg/kg dose level, 3 subjects experienced 1 dose-limiting toxicity (DLT) each. Because the protocol specified that intermediate dose levels could be evaluated, the Data Monitoring Committee (DMC) recommended to include 3 subjects on 2.0 mg/kg, which was not a pre-planned dose level in the protocol. None of the subjects on the 2.0 mg/kg dose level experienced DLTs and, therefore, 2.0 mg/kg was identified as the recommended phase 2 dose (RP2D) for the Expansion Part.

In study GEN702 a more aggressive posology was used. This was a safety trial of tisotumab vedotin dosed 3q4w (Days 1, 8 and 15 of each 28-day cycle) in a mixed population of patients with solid tumours known to express tissue factor (TF). RP2D from the Dose Escalation part was established at 1.2 mg/kg 3q4w. However, in the dose expansion part, severe ocular toxicity was observed at 1.2 mg/kg 3q4w. Thereafter patients enrolling received 2.0 mg/kg Q3W only. 14 patients continued on the 1.2 mg/kg 3q4w, however the overall incidence and severity of adverse effects were higher for that group than for the patients on the 2 mg/kg Q3W regime.

Influence of Immunogenicity on ADC and MMAE PK

Overall, incidence of immunogenicity was low, with no clinically meaningful effect on tisotumab vedotin PK.

Intra- and inter-individual variability

Table 30 . Cycle 1 Pharmacokinetic Parameters for tisotumab vedotin (2.0 mg/kg Q3W) in Protocol SGNTV-001 (PK Analysis Set)

	CRC N=25	PAN N=16	NSCLC N=12	SCCHN N=30	Total N=83
AUC_{inf_p} (day*µg/mL)					
n/M	24/24	16/16	11/11	25/25	76/76
GM (%CV)	59.85 (30)	55.75 (21)	58.78 (30)	57.53 (26)	58.05 (27)
C_{max} (µg/mL)					
n/M	25/25	16/16	11/11	29/29	81/81
GM (%CV)	46.10 (28)	41.65 (23)	42.90 (29)	38.45 (23)	41.93 (26)
T_{max} (day)					
n/M	25/25	16/16	11/11	29/29	81/81
Median	0.03	0.03	0.03	0.04	0.03
Min, max	0.0, 0.1	0.0, 0.1	0.0, 0.1	0.0, 0.1	0.0, 0.1

AUC_{inf_p}=AUC from dosing time extrapolated to infinity, based on the last predicted concentration; CV%=percent coefficient of variation, GM=Geometric mean; n/M=number of samples with calculable parameter/number of subjects with sample tested.

Table 31 . Cycle 1 PK Parameters for TAb in Protocol SGNTV001 (PK Analysis Set)

Parameter	CRC N=25	PAN N=16	NSCLC N=12	SCCHN N=30	Total N=83
AUC_{inf_p} (day*µg/mL)					
n/M	22/22	16/16	12/12	23/23	73/73
GM (%CV)	90.56 (28)	76.43 (24)	84.00 (36)	81.78 (27)	83.46 (29)
C_{max} (µg/mL)					
n/M	25/25	16/16	12/12	28/28	81/81
GM (%CV)	42.65 (25)	37.92 (21)	42.66 (23)	39.53 (18)	40.59 (22)
T_{max} (day)					
n/M	25/25	16/16	12/12	28/28	81/81
Median	0.03	0.03	0.03	0.05	0.03
Min, max	0.0, 0.1	0.0, 0.1	0.0, 0.1	0.0, 0.2	0.0, 0.2

AUC_{inf_p}=AUC from dosing time extrapolated to infinity, based on the last predicted concentration; %CV=Coefficient of variation; GM=Geometric mean; n/M=number of samples with calculable parameter/number of subjects with sample tested.

Tisotumab vedotin (ADC) and TAB concentrations appear to decrease multiexponentially following the end of infusion. The -C_{max} of tisotumab vedotin and TAB occurred shortly after the end of infusion. PK parameter estimates for tisotumab vedotin were similar across cohorts showing low to intermediate inter-subject variability.

MMAE concentrations increased following infusion and reached maximum concentrations ~2 days after infusion. PK parameter estimates for MMAE were similar across cohorts, though large inter-subject variability is observed.

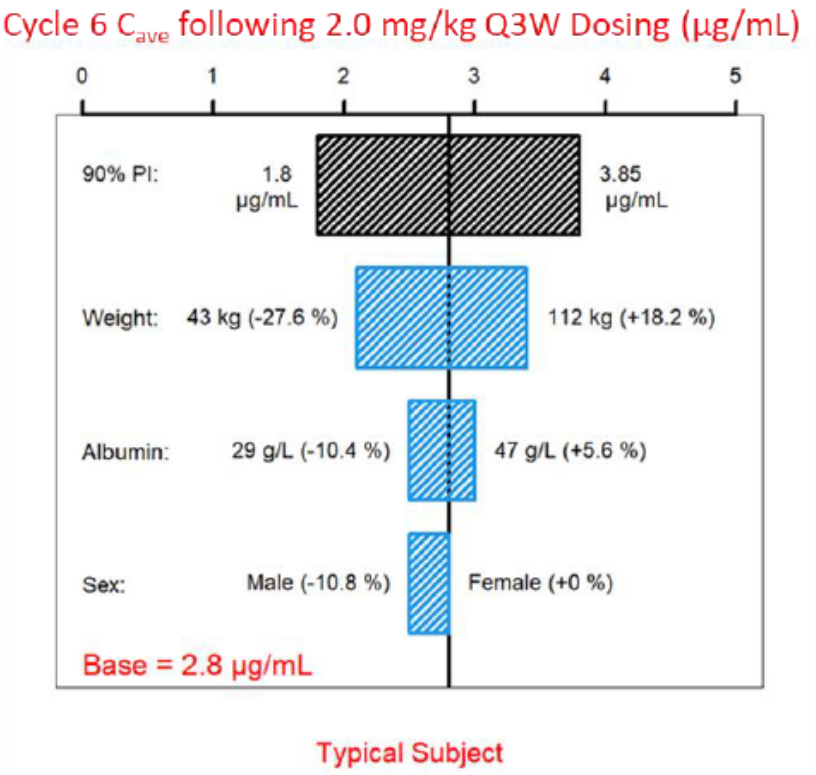
Table 32 . Cycle 1 Pharmacokinetic Parameters for MMAE in Protocol SGNTV-001 (PK Analysis Set)

Parameter	CRC N=25	PAN N=16	NSCLC N=12	SCCHN N=30	Total N=83
AUC_{last} (day*ng/mL)					
n/M	24/24	16/16	12/12	28/28	80/80
GM (%CV)	27.81 (60)	19.16 (82)	34.14 (78)	34.45 (71)	28.69 (74)
C_{max} (ng/mL)					
n/M	25/25	16/16	12/12	29/29	82/82
GM (%CV)	3.43 (53)	2.64 (63)	4.76 (69)	4.45 (70)	3.75 (67)
C_{trough} (ng/mL)					
n /M	18/18	10/10	9/9	23/23	60/60
GM (%CV)	0.11 (80)	0.05 (68)	0.08 (82)	0.1 (88)	0.09 (86)
T_{max} (day)					
n/M	25/25	16/16	12/12	29/29	82/82
Median	2.02	1.99	2.00	2.01	2.01
Min, max	1.9, 8.0	0.9, 7.0	1.8, 6.9	0.9, 7.2	0.9, 8.0

AUC_{last}=AUC from time zero to the last measurable concentration; %CV=Coefficient of variation; C_{trough}=the concentration reached by a drug immediately before the next dose is administered; GM=Geometric mean; n/M=number of samples with calculable parameter/number of subjects with sample tested.

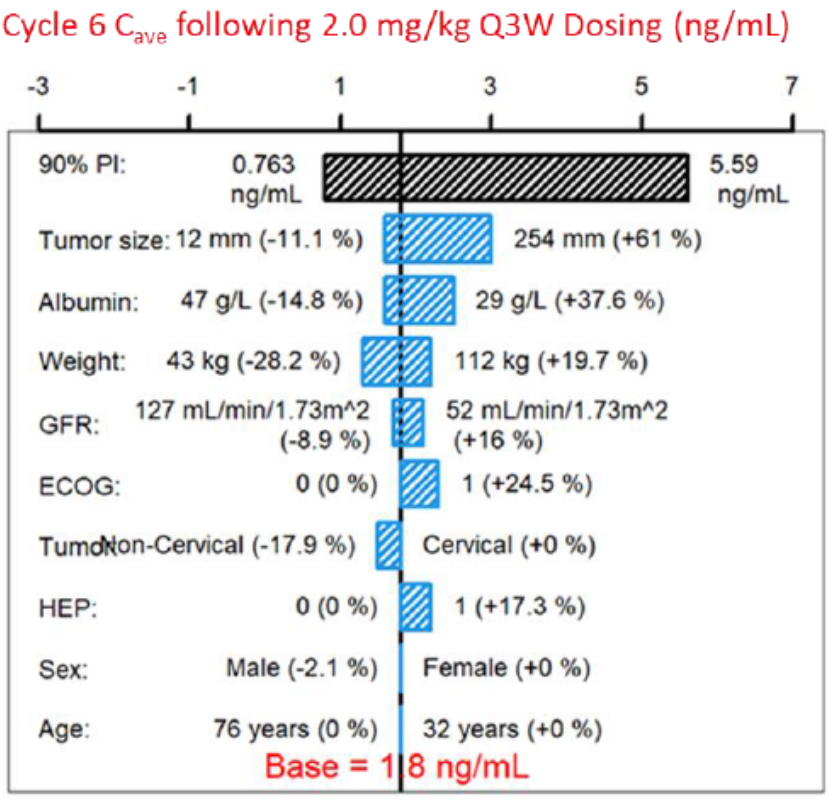
Special populations

Age, sex, renal function, ECOG score, baseline TF expression, ADA status, and geographic region (Europe versus US) had no meaningful effect on ADC and MMAE exposure, see Figure 22 and Figure 23.



Base (black vertical line and red text): predicted Cycle 6 exposure in a typical subject following 2.0 mg/kg Q3W doses (with 200 mg cap). **Black shaded bar**: exposure range correspond to 5th and 95th percentiles of exposure distribution. **Blue shaded bars**: influence of each single covariate on the Cycle 6 exposure. For each continuous covariate, 2 subjects were generated with extreme covariate values (2.5th and 97.5th percentile). For each categorical covariate, 1 subject from each category was created; other covariates were fixed at the reference category. The length of each bar describes the potential impact of that particular covariate on ADC exposure, with the percentage values representing the percent change of exposure from the base. The most influential covariate is at the top of the plot. **This covariate effect was checked one covariate at a time against the typical (reference) subject. Typical subject is defined as a 70-kg, 60 years old female patient with cervical cancer and baseline tumor burden of 60 mm, ECOG 0, no hepatic impairment, and eGFR of 90mL/min/1.73m^2.**

Figure 10 Effects of Covariates on Steady-State ADC Exposure



Typical Subject

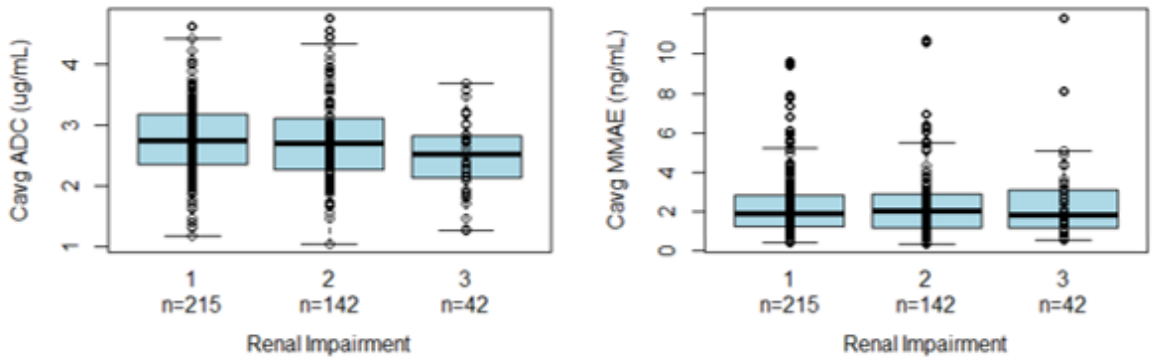
Base (black vertical line and red text): predicted Cycle 6 exposure in a typical subject following 2.0 mg/kg Q3W doses (with 200 mg cap). **Black shaded bar**: exposure range correspond to 5th and 95th percentiles of exposure distribution. **Blue shaded bars**: influence of each single covariate on the Cycle 6 exposure. For each continuous covariate, 2 subjects were generated with extreme covariate values (2.5th and 97.5th percentile). For each categorical covariate, 1 subject from each category was created; other covariates were fixed at the reference category. The length of each bar describes the potential impact of that particular covariate on MMAE exposure, with the percentage values representing the percent change of exposure from the base. The most influential covariate is at the top of the plot. Hepatic (HEP) impairment: 0=Normal hepatic function; 1=mild impairment
This covariate effect was checked one covariate at a time against the typical (reference) subject. Typical subject is defined as a 70-kg, 60 years old female patient with cervical cancer and baseline tumor burden of 60 mm, ECOG 0, no hepatic impairment, and GFR of 90mL/min/1.73m^2

Figure 11. Effects of Covariates on Steady-State MMAE Exposure

Impaired renal function

No formal clinical study has been conducted to assess the effect of renal function on the PK of tisotumab vedotin.

The effect of mild and moderate renal impairment on tisotumab vedotin and unconjugated MMAE exposure was assessed using the PopPK model, see Figure 24.1. The assessment of renal impairment was based on estimated creatinine clearance (CrCl) at baseline as determined using the Cockcroft Gault Formula (Cockcroft 1976) and categorised as mild (CrCl ≥60 to <90 mL/min), moderate (CrCl 30 to <60 mL/min) or severe (CrCl <30 mL/min). Derivation of baseline creatinine was based on the central lab results. Based on enrolment criteria for the tisotumab vedotin clinical studies, enrolled subjects had either normal renal function, mild renal impairment, or moderate renal impairment.



Renal Impairment: 1=normal renal function; 2=mild renal impairment; 3=moderate renal impairment
Source: PopPK Report SR1015-248, Figure 113

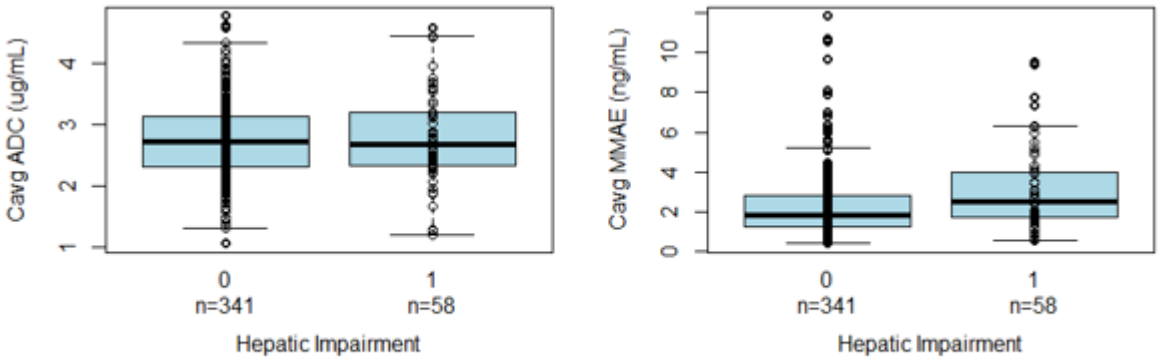
Figure 12 Effect of Renal Impairment: Model predicted ADC and MMAE Cycle 1 Exposures (2.0 mg/kg Q3W with 200 mg Cap)

Impaired hepatic function

No formal clinical study has been conducted to assess the effect of hepatic function on the PK of tisotumab vedotin.

The effect of mild hepatic impairment on tisotumab vedotin and unconjugated MMAE exposure was assessed using the PopPK model, see Figure 25.

Individual model predicted Cycle 1 exposures based on 2.0 mg/kg tisotumab vedotin Q3W (up to 200 mg for a body weight ≥100 kg) were compared between subjects with normal hepatic function and those with mild hepatic impairment. Predicted ADC exposure for subjects with mild hepatic impairment was similar to subjects with normal hepatic function, while MMAE exposures were 37% higher. The range of both ADC and MMAE exposures was similar between the 2 groups. Subjects who had mild hepatic impairment did not appear to have a notably increased incidence of treatment emergent SAEs, or Grade 3 and higher TEAEs, indicating the increase of MMAE exposure in mild hepatic impairment subjects is not clinically meaningful.



Hepatic impairment: 0=Normal hepatic function; 1=mild impairment
Source: PopPK Report SR1015-248, Figure 113

Figure 13 Effect of Hepatic Impairment: Model predicted ADC and MMAE Cycle 1 Exposures (2.0 mg/kg Q3W with 200 mg Cap)

Weight

The PopPK results are shown below.

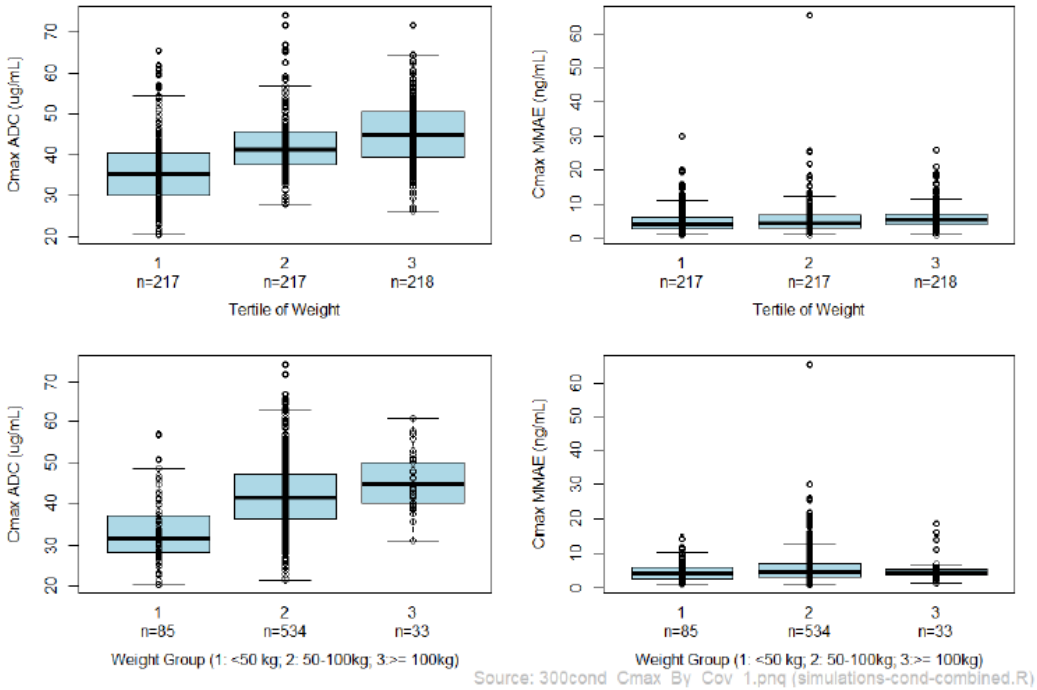


Figure 14. Predicted ADC and MMAE Cycle 1 C_{max} versus Tertiles Weight Groups (2 mg/kg Q3W with 200 mg Cap). Source; Figure 93 in the POPPK report.

Elderly

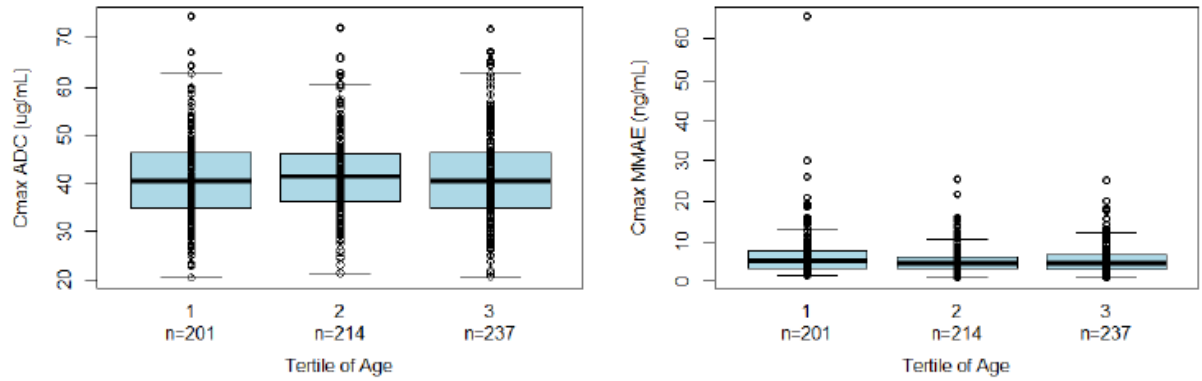


Figure 15. Predicted ADC and MMAE Cycle 1 C_{max} versus Tertiles of Age Groups (2 mg/kg Q3W with 200 mg Cap). Source; Figure 93 in POPPK report.

Tertiles of age were tested as a covariate in the POPPK model. No difference in C_{max} of ADC or MMAE was observed.

Table 33 Age ranges studies in the elderly population

	Age 65-74 (Older subjects number/total number)	Age 75-84 (Older subjects number/total number)	Age 85+ (Older subjects number/total number)
GEN701	49/195	8/195	0/195
GEN702	8/33	0/33	0/33
SGNTV-001	20/70	7/70	0/70
GCT1015-04	11/101	2/101	0/101
GCT1015-06	4/23	0/23	0/23
SGNTV-003	33/230	8/230	0/230

Pharmacokinetic interaction studies

- *In vitro* metabolism of MMAE in human hepatocytes generated the same metabolites observed in rat and monkey *in vitro* assays.
- MMAE was identified as a substrate of CYP3A4 *in vitro* by using a panel of recombinant human CYP enzymes. In humans, coadministration of brentuximab vedotin with a strong CYP3A4/5 inhibitor (ketoconazole) increased MMAE exposures by 34%, and a CYP3A4/5 inducer (rifampin) decreased MMAE exposures by 46% (Han 2013).
- MMAE is not a potent reversible inhibitor or inducer of CYP3A4/5, but it is a quasi-irreversible, metabolism-based CYP3A4/5 inhibitor. Considering the low MMAE serum mean C_{max} in humans (approximately 8 nM or 4-6 ng/mL) and much higher kinetic interaction coefficient (K_I) (1.12 µM), MMAE is not expected to alter the PK of other CYP3A4/5 substrate drugs markedly. In humans, coadministration of another ADC with MMAE, namely brentuximab vedotin did not affect exposure to midazolam, a CYP3A4/5 substrate (Han 2013).

Results from *in vitro* studies suggest that MMAE is a substrate of P-gp but not a substrate of BCRP, MRP2, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3. Furthermore, MMAE is not an inhibitor of P-gp, BCRP, BSEP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations

Pharmacokinetics using human biomaterials

Table 34: Summary of in vitro enzyme inhibition

Enzyme	CYP reaction	Competitive inhibition		TDI		Positive signal to evaluate further
		IC50 (µM)	K_I (µM)	IC50 (µM)	K_{inact} (min^{-1})	Yes/No
CYP1A2	Phenacetin *O*-deethylation	>100	NA	>100	NA	No
CYP2B6	Bupropion hydroxylation	>100	NA	>100	NA	No
CYP2C8	Amodiaquine *N*-dealkylation	>100	NA	>100	NA	No
CYP2C9	Diclofenac 4´-hydroxylation	>100	NA	>100	NA	No

CYP2C19	*S*Mephenytoin- 4´-hydroxylation	>100	NA	>100	NA	No
CYP2D6	Dextromethorphan *O*-demethylation	>100	NA	>100	NA	No
CYP3A4	Testosterone 6β-hydroxylation	>100	1.12	0.6	0.10 (min^{-1})	Yes
CYP3A4	Midazolam 1´-hydroxylation	10	NR	0.4	NR	Yes

NR: Not reported

Time dependent inhibition of CYP3A4/5 as measured by testosterone 6βhydroxylation was found to be partially reversed with microsomal reisolation- and fully reversed with treatment by potassium ferricyanide prior to -reisolation-. MMAE was found to form a metabolite inhibitory complex with CYP3A4/5.

Table 35:Summary of in vitro enzyme induction

	Fold induction mRNA								
	CYP1A2			CYP2B6			CYP3A4		
	H1165	H1167	H1169	H1165	H1167	H1169	H1165	H1167	H1169
DMSO 0.1 %	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
MMAE 1 nM	0.941	1.47	0.964	0.982	1.39	0.859	1.32	1.56	1.34
MMAE 10 nM	1.17	1.57	0.695	1.09	1.19	0.783	1.94	1.66	1.21
MMAE 100 nM	0.197	0.130	0.0940	0.110	0.108	0.0800	0.697	0.280	0.188
MMAE 1000 nM	0.0280	0.0280	0.0210	0.0200	0.0390	0.0320	0.0780	0.0390	0.0380
Flumazenil 25 µM	0.898	1.29	1.06	0.832	1.57	1.16	0.631	1.57	1.24
Omeprazole 50 µM	23.1	160	70.9	6.38	7.45	8.43	6.97	10.0	15.7

Table 36: In vitro transporter inhibition

Transporter	Substrate	In vitro system[a]	IC50 (µM)	Positive signal (Y/N)
P-gp	Digoxin	Caco-2	>50 µM	No
BCRP	Estrone-3-sulfate	Vesicular transport assay	>5 µM	No
OATP1B1	Estradiol-17-β-glucuronide	Uptake transporter assay	>5 µM	No
OATP1B3	Cholecystokinin-octapeptide	Uptake transporter assay	>5 µM	No
OAT1	Tenofovir	Uptake transporter assay	>5 µM	No
OAT3	Estrone-3-sulfate	Uptake transporter assay	>5 µM	No
OCT2	Metformin	Uptake transporter assay	>5 µM	No
OCT1	Metformin	Uptake transporter assay	>5 µM	No
MATE1	NT	Uptake transporter assay	>5 µM	No
MATE2	NT	Uptake transporter assay	>5 µM	No
MRP2	Estradiol-17-β-glucuronide	Vesicular transport	>5 µM	No
BSEP	Taurocholate	Vesicular transport	>5 µM	No

Vesicular transport assays were performed with inside out membrane vesicles prepared from cells overexpressing human ABC transporters BCRP, BSEP, and MRP2. Uptake experiments were performed using CHO or HEK293 cells stably expressing the respective human uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2. NT: Not tested.

In vivo drug-drug interaction studies

No dedicated *in vivo* drug-drug interaction studies were conducted with tisotumab vedotin. Instead a study on brentuximab vedotin was presented in a publication by Han et al from 2013.

Brentuximab vedotin is an antibody–drug conjugate (ADC) that selectively delivers monomethyl auristatin E (MMAE) into CD30-expressing cells. The linker and mechanism of intracellular release of MMAE is the same for brentuximab vedotin and tisotumab vedotin. This study evaluated the CYP3A-mediated drug–drug interaction potential of brentuximab vedotin and the excretion of MMAE.

Effects of Brentuximab Vedotin on Midazolam PK Parameters and Effects of Rifampin and Ketoconazole on Brentuximab Vedotin PK Parameters are presented in the table below.

Table 37. Effects of Brentuximab Vedotin on Midazolam PK Parameters and Effects of Rifampin and Ketoconazole on Brentuximab Vedotin PK Parameters (Han 2013)

		Geometric mean (% CV)[a]		
Evaluation (analyte PK parameter)	n	Alone	Combination	GMR (90% CI)
Midazolam with or without brentuximab vedotin				
Midazolam				
$AUC_{0-\infty}$ (h μg/mL)	15	0.079 (92)	0.074 (74)	0.94 (0.81–1.10)[b]
C_{max} (μg/mL)	14	0.073 (116)	0.084 (176)	1.15 (0.76–1.74)[b]
T_{max} (h)	14	0.050 (0.00, 0.27)[a]	0.042 (0.03, 0.28)[a]	—
$t_{1/2}$ (h)	15	6.40 (48)	5.69 (38)	—
Brentuximab vedotin with or without rifampin				
ADC				
$AUC_{0-\infty}$ (d μg/mL)	11	89.84 (25)	93.40 (42)	1.04 (0.87–1.24)[c]
C_{max} (μg/mL)	11	36.74 (34)	34.05 (32)	0.93 (0.81–1.06)[c]
T_{max} (d)	11	0.02 (0.02, 0.09)[a]	0.02 (0.02, 0.08)[a]	—
$t_{1/2}$ (d)	11	5.87 (66)	6.73 (58)	—
MMAE				
$AUC_{0-\infty}$ (d ng/mL)	14	40.06 (53)	21.54 (38)	0.54 (0.43–0.68)[c]
C_{max} (ng/mL)	14	4.98 (67)	2.80 (36)	0.56 (0.42–0.76)[c]
T_{max} (d)	14	3.00 (0.99, 5.01)[a]	1.49 (0.33, 4.02)[a]	—
$t_{1/2}$ (d)	14	3.71 (19)	3.66 (17)	—
Brentuximab vedotin with or without ketoconazole				
ADC				
$AUC_{0-\infty}$ (d μg/mL)	11	52.77 (28)	56.26 (40)	1.07 (0.95–1.19)[d]
C_{max} (μg/mL)	16	22.57 (23)	22.38 (70)	0.99 (0.75–1.31)[d]
T_{max} (d)	16	0.02 (0.02, 0.17)[a]	0.02 (0.02, 0.25)[a]	—
$t_{1/2}$ (d)	11	5.70 (33)	5.45 (31)	—
MMAE				
$AUC_{0-\infty}$ (d ng/mL)	14	26.65 (71)	35.72 (126)	1.34 (0.98–1.84)[d]
C_{max} (ng/mL)	16	4.11 (71)	5.13 (114)	1.25 (0.90–1.72)[d]
T_{max} (d)	16	1.97 (0.97, 6.99)[a]	2.45 (0.22, 4.06)[a]	—
$t_{1/2}$ (d)	14	3.06 (13)	3.47 (66)	—

GMR, geometric mean ratio; CI, confidence interval; CV, coefficient of variation.
[a]Geometric mean (%CV) presented for $AUC_{0-\infty}$, C_{max}, and $t_{1/2}$. Median (range) presented for T_{max}.
[b]Geometric mean ratio of midazolam + brentuximab vedotin/midazolam alone.
[c]Geometric mean ratio of brentuximab vedotin with rifampin/brentuximab vedotin alone.
[d]Geometric mean ratio of brentuximab vedotin with ketoconazole/brentuximab vedotin alone.

Table 38: Summary of clinical DDI studies

Comparison	Substance Ratio, as Percent (90% CI)		Dosing Recommendation
	C_{max}	A,UC_{inf}	
Victim			

Effect of co-administration with ketoconazole (inhibitor)	125 (90–172)	134 (98–184)	No adjustment initially. However, monitoring for adverse effects should be increased.
Effect of co-administration with rifampin (inducer)	56 (42–76)	0.54 (0.43–0.68)	No adjustment
Perpetrator			
Effect on midazolam	1.15 (0.76–1.74)	0.94 (0.81–1.10)	No adjustment

2.4.2.2. Pharmacodynamics

Primary and Secondary pharmacology

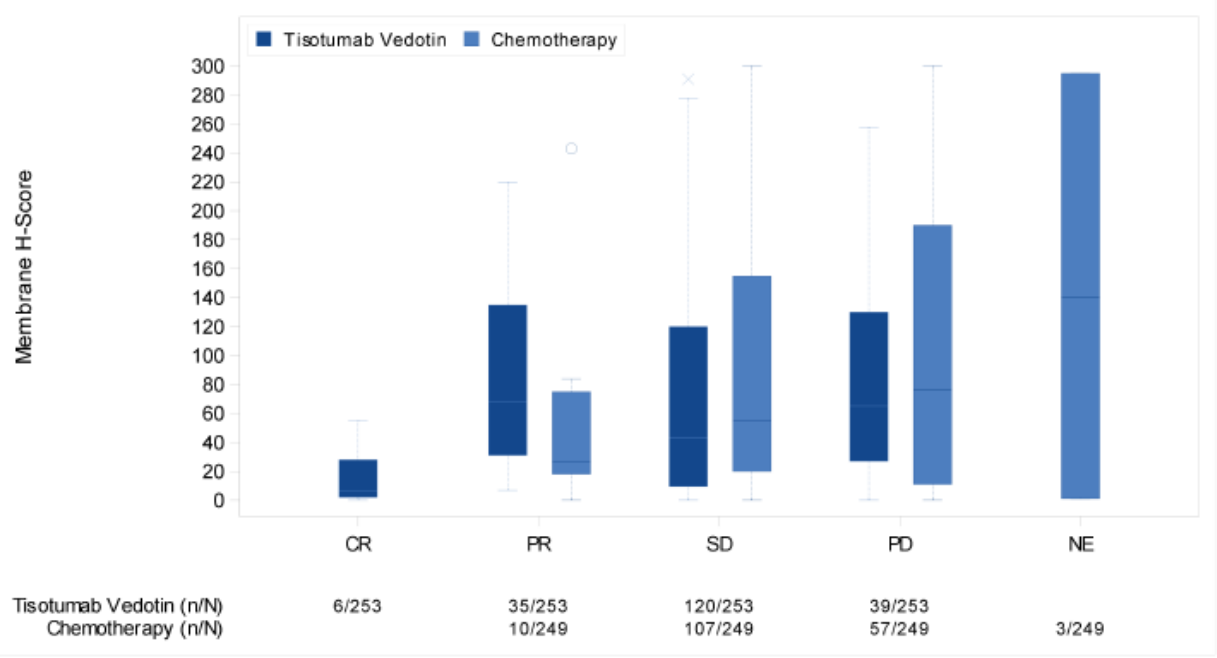
No primary pharmacology studies have been performed. No formal DDI studies have been conducted with tisotumab vedotin.

However, baseline tumour TF expression was retrospectively assessed, using a validated immunohistochemistry (IHC) assay, from tumour biopsies collected from subjects enrolled in study SGNTV-003 with r/mCC prior to treatment.

Table 39 TF Tumour Membrane H-Score in Study SGNTV-003

	Tisotumab Vedotin (N=253)	Chemotherapy (N=249)
Subjects with evaluable baseline biopsy, n (%)	210 (83.0)	194 (77.9)
Mean Tumor Membrane H-score (STD)	76.8 (74.7)	92.8 (86.6)
Median Tumor Membrane H-score (range)	45.0 (0, 291)	65.0 (0, 300)

Figure 16 TF Expression in Tumour Membrane H-Score at Baseline by Confrimed Best Overall Response as assessed by investigator by Treatment Arn (SGNTC-003 ITT Analysis Set)



Whiskers extend to the most extreme observation within 1.5 times the interquartile range from the nearest quartile.
x denotes the outlier for tisotumab vedotin arm and o denotes the outlier for chemotherapy arm.
Subjects with BOR as NA are excluded from the output.
Snapshot Date: 21AUG2023, DCO Date: 24JUL2023

In both arms, the distribution of TF expression overlapped across all response categories.

c-QTc analyses

ECG measures and corresponding PK samples were collected from 153 patients with solid cancers in studies SGNTV-001 (N=55) and GCT1015-04 (N=98) following a dose of 2.0 mg/kg Q3W tisotumab vedotin. Study SGNTV-001 data included one ΔQTcF observation per patient while data from Study GCT1015-04 included approximately 12 ΔQTcF observations per patient (Table 40, Table 41).

Table 40 Studies Included in the Concentration QTc Analysis

The cutoff date for data inclusion for both studies was 08/22/2019.

Study	Description	Population	N	Dosing and Frequency	Paired PK-QT Measurements
GCT1015-04 Pivotal Phase 2	Single-arm, open-label TV; ongoing	Previously treated recurrent or metastatic cervical cancer	98	2.0 mg/kg Q3W (with 200 mg cap)	Cycle 1 Day 1 predose; Cycle 1 Day 1 end of infusion; Cycle 1 Day 4; Cycle 1 Day 8; all other doses: pre-dose, end of infusion
SGNTV-001 Phase 2 [a]	Open-label TV; ongoing	Locally advanced or metastatic solid tumor types known to express TF	55	2.0 mg/kg Q3W (with 200 mg cap)	Cycle 1 Day 1 predose Cycle 1 Day 3

[a] Only subjects from US sites were included, as sites from other countires did not perform triplicate ECGs.

Table 41 Number of Patients, QTcF and PK assessment by Dose and Study

Study	Statistic	All ΔQTcF	ΔQTcF pairs with	
			ADC	MMAE
SGNTV-001	Number of observations	55	55	55
	Number of patients	55	55	55
GCT1015-04	Number of observations	1152	1137	1141
	Number of patients	98	98	98
Combined	Number of observations	1207	1192	1196
	Number of patients	153	153	153

Source: Table2.csv (Prepare_QTc_Data_07_27_2020.R)

Tables below gives a summary of observed ECG changes in Study GCT1015-04 and Study SGNTV-001. No subjects in either study who experienced a post-baseline ΔQTcF >30 ms experienced any clinically meaningful cardiac events.

Table 42 GCT1015-04 Categorical Analysis for QtcF Changes from Baseline

	Tisotumab Vedotin 2.0 mg/kg (N=101) n (%)
Subjects with baseline and at least one post-baseline measure of QTcF	98 (97.0)
QTcF Change from baseline (>10 ms and <=20ms) for any post-baseline visits	76 (75.2)
QTcF Change from baseline (>20 ms and <=30ms) for any post-baseline visits	36 (35.6)
QTcF Change from baseline (>30 ms and <=60ms) for any post-baseline visits	18 (17.8)
QTcF Change from baseline (>60 ms) for any post-baseline visits	2 (2.0)
Subjects with post-baseline measure of QTcF	
>480 ms	1 (1.0)
>500 ms	0

Source: Table 14.03.25b

Table 43 SGNTV-001 (Part A) ECG Categorical Analysis for QtcF Changes from Baseline

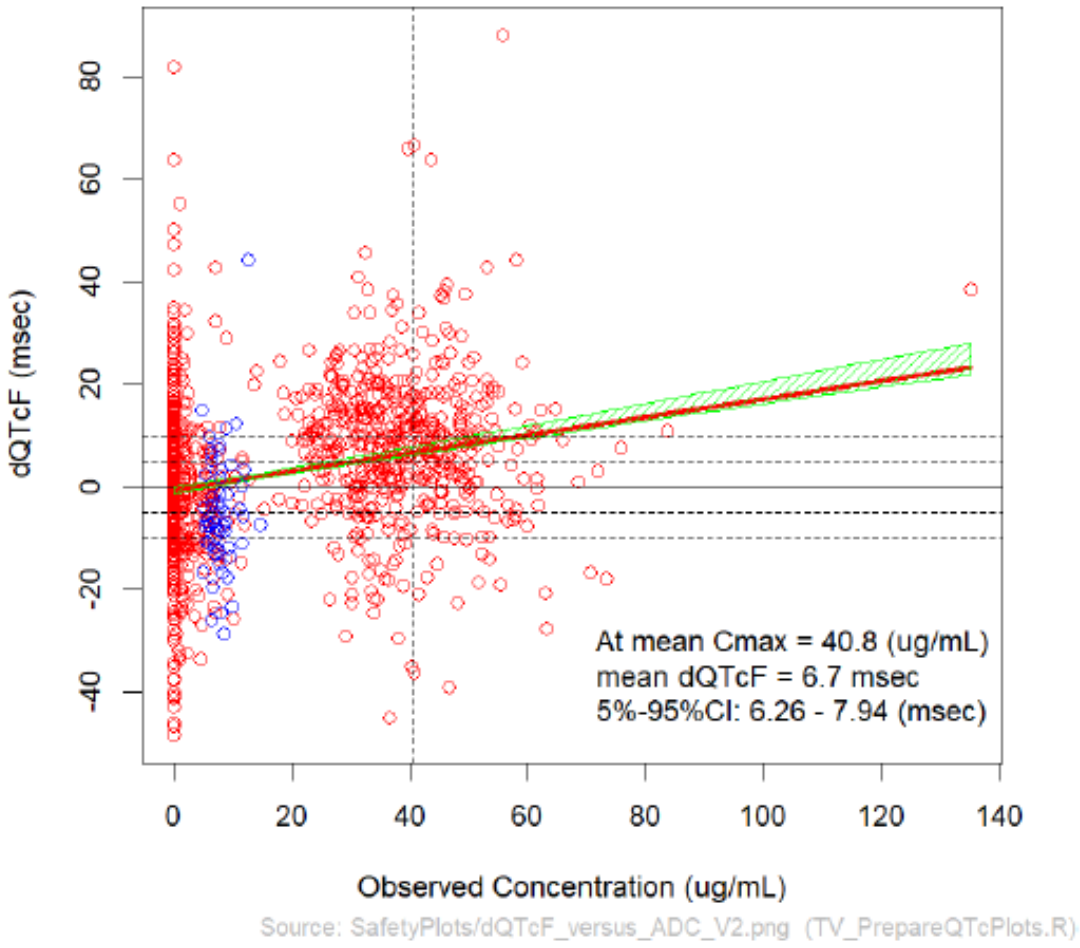
	Tisotumab Vedotin 2.0 mg/kg (N=89) n (%)
Subjects with baseline and at least one post-baseline measure of QTcF	66 (74.2)
QTcF Change from baseline (>10 ms and <=20ms) for any post-baseline visits	4 (4.5)
QTcF Change from baseline (>20 ms and <=30ms) for any post-baseline visits	0
QTcF Change from baseline (>30 ms and <=60ms) for any post-baseline visits	2 (2.2)
QTcF Change from baseline (>60 ms) for any post-baseline visits	0
Subjects with post-baseline measure of QTcF	
>480 ms	0
>500 ms	0

Source: Table 14.03.25c

The c-QTc relation was explored by linear mixed-effects models of ΔQTcF versus observed concentrations of ADC or MMAE. The ECG measurement at pre-dose on Cycle 1 Day 1 was used as a baseline. BQL data were set to 0; missing PK measurements were set to missing. Data from unscheduled and EOF visits were excluded from the analysis. Data points were excluded from the c-QTc analyses if either the ECG or PK observation was missing. The predicted ΔQTcF - concentration relationship and its upper one-sided 95% confidence interval was constructed by simulation using bootstrap (n=1000) at the predicted mean Cycle 6 C_{max} value. Figure 29 and Figure 30 show the model predicted concentration- ΔQTcF relationship for ADC and MMAE, respectively with observations.

Figure 17 Concentration ΔQTcF relationship for ADC, Study GCT1015-04

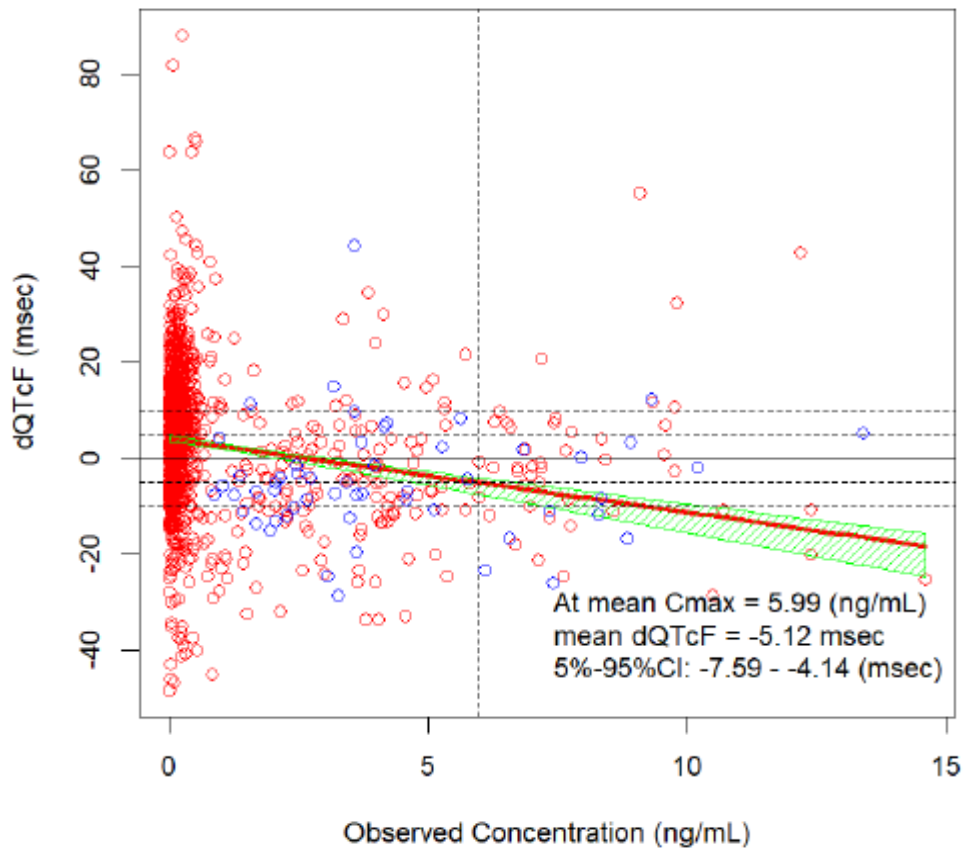
Patients from Study GCT1015-04 (red circles) were included in the analysis. Data for patients from Study SGNTV-001 (blue circles) are shown for illustration only. Bold red line: model prediction; green shaded area: 5% and 95% bounds of the confidence interval for model predictions computed using bootstrap procedure; dashed horizontal lines (at y = -10, 5, 0, 5, 10) are provided for reference; the dashed vertical line illustrates mean predicted C_{max} of 40.8 ug/mL.

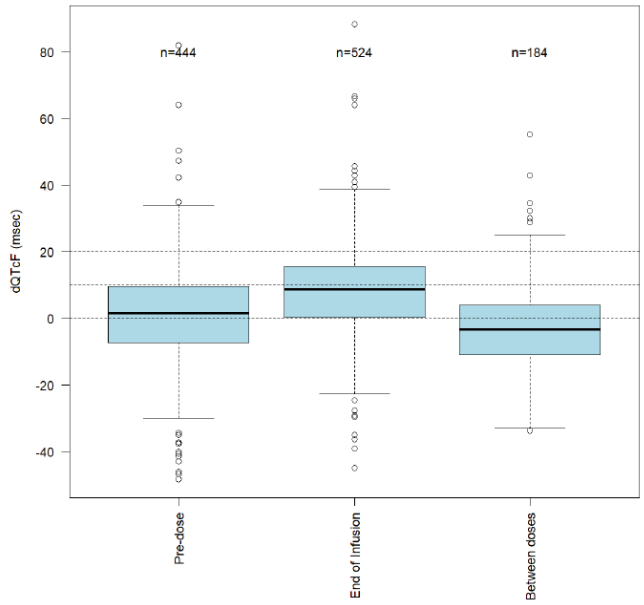


Source: SafetyPlots/dQTcF_versus_ADC_V2.png (TV_PrepareQTcPlots.R)

Figure 18 Concentration ΔQTcF relationship for MMAE, Study GCT1015-04

Patients from Study GCT1015-04 (red circles) were included in the analysis. Data for patients from Study SGNTV-001 (blue circles) are shown for illustration only. Bold red line: model prediction; green shaded area: 5% and 95% bounds of the confidence interval for model predictions computed using bootstrap procedure; dashed horizontal lines (at y = -10, 5, 0, 5, 10) are provided for reference; the dashed vertical line illustrates mean predicted C_{max} of 5.99 ng/mL.





The dQTcF values are plotted versus time point using box and whisker plots. Median values of the observed dQTcF are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Circles show the observations-outliers defined as those beyond 1.5*IQR. Dashed lines at y = 0, 10, and 20 msec are included for reference.

Pre-dose: all pre-dose values observed from the end of Cycle 1 to the end of Cycle 18.

End of Infusion: all end of infusion values observed from Cycle 1 to Cycle 18.

Between doses: the joint distribution observed during Cycle 1 Day 4 and Cycle 1 Day 8 visits.

The numbers on the top of the plot show the number of observations in each category.

Figure 19 Observed dQTcF versus visit timepoints from Studay GCT1015-04

Individual plots of Total Ab, ADC or MMAE concentrations versus QTcF change from baseline from Study GCT1015-04 are varied, with no consistent evidence of a time-delay. The linear modeling applied does not account for time-delay. A selection of hysteresis plots from 92 individuals from Study GCT1015-04 (3 out of 12) for ADC and MMAE are shown in Figures 5 and 6 respectively. These plots include 4 time points (if all were available for a subject): Cycle 1 EOI, Cycle 1 Day 4, Cycle 1 Day 8, Cycle 2 pre-dose. The arrows show the direction of time.

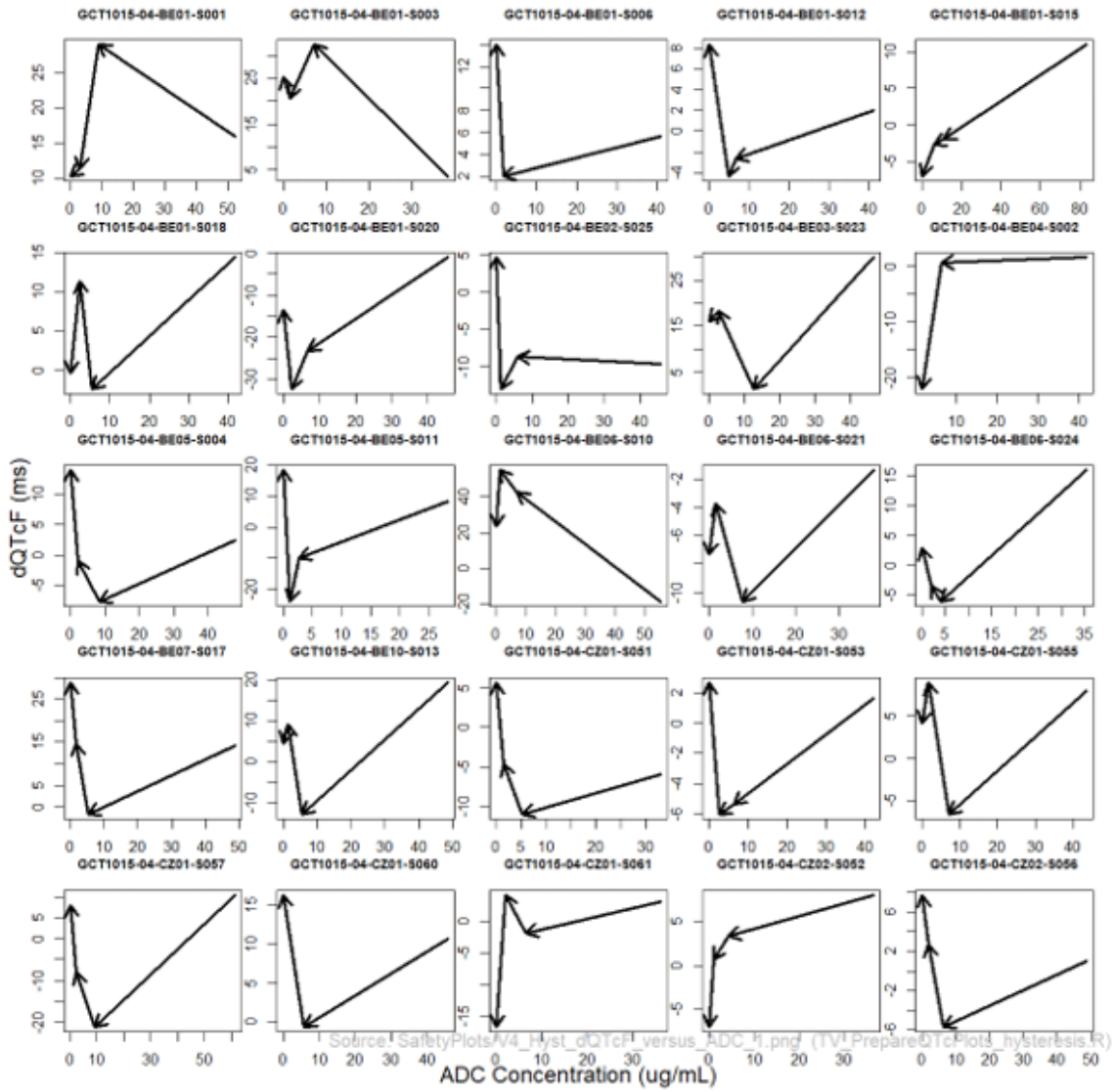


Figure 20 Individual Hysteresis plots of dQTcF versus ADC concentrations

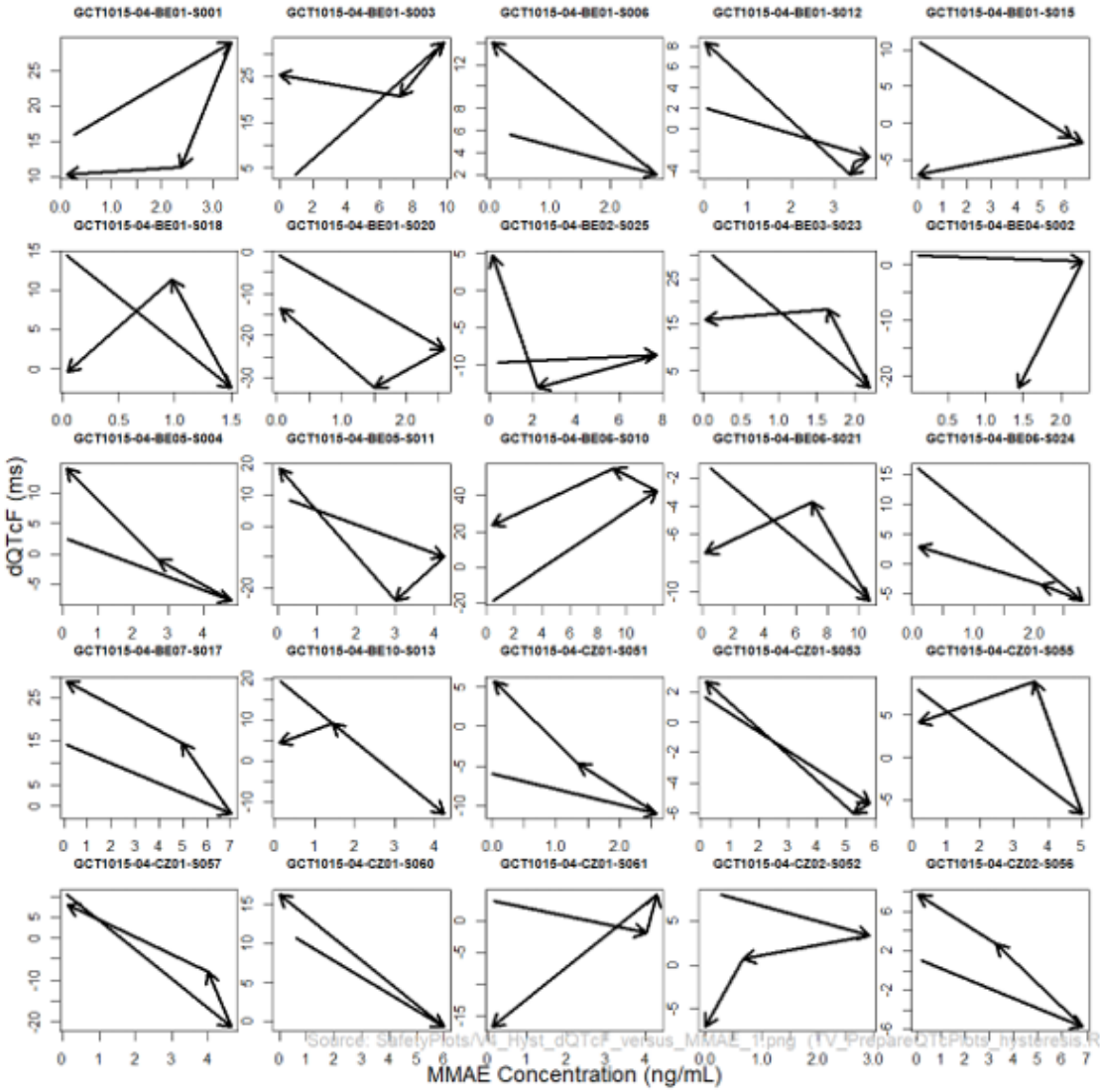


Figure 21 Individual Hysteresis plots of dQTcF versus MMAE concentrations

Anti-drug antibodies (ADA)

Table 44: Summary of ADA incidence (Integrated ADA evaluation set)

	SGNTV-003		GCT1015-04	All Cervical [a]	All Tumor Types[b]
	Tisotumab vedotin N=211 n (%)	Chemotherapy N=0 n (%)	2.0 mg/kg N=93 n (%)	at 2.0 mg/kg N=372 n (%)	at 2.0 mg/kg N=551 n (%)
Subjects ADA negative at baseline[c]	197	NA	91	355	525
Positive[d]	12 (5.7)	NA	5 (5.4)	21 (5.6)	27 (4.9)
Subjects ADA positive at baseline[c]	14	NA	2	17	26
Treatment boosted [e]	0 (0)	NA	0 (0)	0 (0)	1 (0.2)

ADA evaluable set includes subjects who received tisotumab vedotin at 2.0 mg/kg Q3W and have a baseline ADA status and at least one ADA sample evaluated at post treatment.
GEN701, GCT1015-06 includes subjects who received tisotumab vedotin at 2.0 mg/kg Q3W from both Dose Escalation and Cohort Expansion.
a. Includes data from studies SGNTV-003, GCT1015-04, GEN701 (Dose Escalation and Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Dose Escalation and Cohort Expansion).
b. Includes data from studies SGNTV-003, GEN701 (Dose Escalation and Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Dose Escalation and Cohort Expansion), and SGNTV-001 (Part A).
c. Baseline is defined as the latest available measurement made before the first treatment with tisotumab vedotin
d. For post-baseline results, a subject is considered ADA positive if either 1) ADA is negative at baseline and at least 1 post-baseline result is positive 2) positive at baseline and at least 1 positive post-baseline result with a titer at least 4 times higher than baseline.
e. "Treatment boosted" refers to subjects with predose positive ADA and have a titer of ≥ 4 times baseline titer on treatment.

Neutralizing drug antibodies (NAb)

In study GCT10-15 Nab were detected in 2 patients. In study SGNTV-003 no Nab were detected.

Exposure-response analyses

Relation of exposure to ORR and safety end-points were investigated using linear logistic regression models, while the relation of ADC exposure to probability of PFS, OS and DOR were explored by multivariate Cox proportional hazard models.

Table 45: Description of the Full Models of Exposure-Response Analyses

Analysis Type	Endpoint	Exposure Measure	Covariate Factors
Exposure-Safety	Probability of adverse event	$AUC_{1,ADC}$ $C_{max1,ADC}$ $AUC_{1,MMAE}$ $C_{max1,MMAE}$	Age
			Weight
			Sex
			Race (Asian versus other)
			Region (US versus other)
			Tumor Type (cervical versus other)
			Baseline tumor size
			Baseline albumin
			Baseline LDH
			Renal impairment category (normal vs mild or moderate [RENAL2] and normal or mild versus moderate [RENAL3])
			Hepatic impairment category (impaired versus normal)
			Baseline ECOG performance status
			Baseline tissue factor H-score
			Presence of ocular AEs at baseline (included only for ocular AEs)
Exposure-Efficacy	Probability of ORR. PFS, OS, DOR.	$AUC_{1,ADC}$ $C_{max1,ADC}$	Age
			Weight
			Race (Asian versus other)
			Region (US versus other)
			Baseline tumor size
			Baseline albumin
			Baseline LDH
			Renal impairment category (RENAL2 and RENAL3)
			Hepatic impairment category (impaired versus normal)
			Baseline ECOG performance status (1+ versus 0)
			Baseline tissue factor H-score
			Histology (squamous/not)
			Prior bevacizumab treatment
			Prior radiation therapy

The objectives of the ER analyses were to characterise the relationships of exposures to tisotumab vedotin with measures of efficacy and the relationships of exposures to tisotumab vedotin and unconjugated MMAE with measures of safety as specified below.

The specific objectives of the exposure efficacy analysis for subjects from Study SGNTV 003 were as follows:

- To describe the relationship of tisotumab vedotin exposure measures with objective response rate (ORR).
- To determine the effect of tisotumab vedotin exposure measures on probability of ORR after accounting for selected key covariates.
- To describe the relationship of tisotumab vedotin exposure measures with duration of objective response (DOR), PFS, and overall survival (OS).
- To determine the effect of tisotumab vedotin exposures on DOR, PFS, and OS after accounting for selected key covariates.

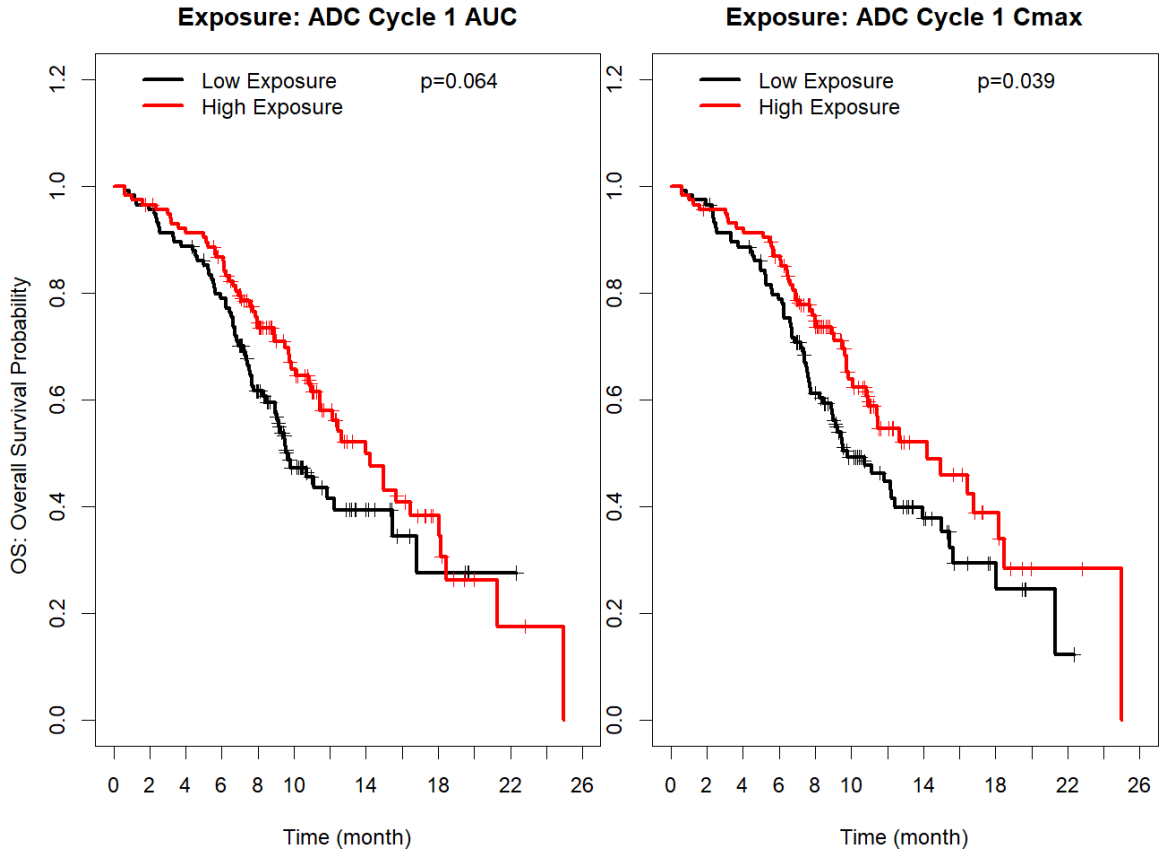
ER analyses were based on PopPK model predictions of tisotumab vedotin and unconjugated MMAE exposures, where individual predicted exposure estimates were merged with corresponding observed subject efficacy and safety responses. Cycle 1 AUC and Cycle 1 Cmax exposure measures were used for ER analyses to avoid potential confounding due to dose delays, reductions, or interruptions. For

ADC, individual predicted Cycle 1 AUC (AUC1,ADC) and Cmax (Cmax1,ADC) were used. For MMAE, individual predicted Cycle 1 AUC (AUC1,MMAE), Cmax (Cmax1,MMAE) as well as the concentration reached by the drug immediately before the next dose was administered (Ctrough) (Ctrough1,MMAE) were used; however, all MMAE exposure measures were strongly correlated (r >0.97), therefore only MMAE Cycle 1 AUC was used in the exposure safety analyses.

Exposure-efficacy relations

The assessment of exposure efficacy response was conducted in a total of 230 subjects with r/mCC who received tisotumab vedotin by IV infusion administered at 2.0 mg/kg Q3W (up to a maximum of 200 mg for subjects ≥100 kg) in the SGNTV 003 study.

Primary endpoint (OS)



Low exposure: ≤ median, High exposure > median. P-value: p-value of the log-rank test comparing subjects with low and high exposure. Source: Figure 4, ER Report TRN-7394; SCP page 58

Figure 22 Kaplan-Meyer Plot by Exposure Group: Time to Death

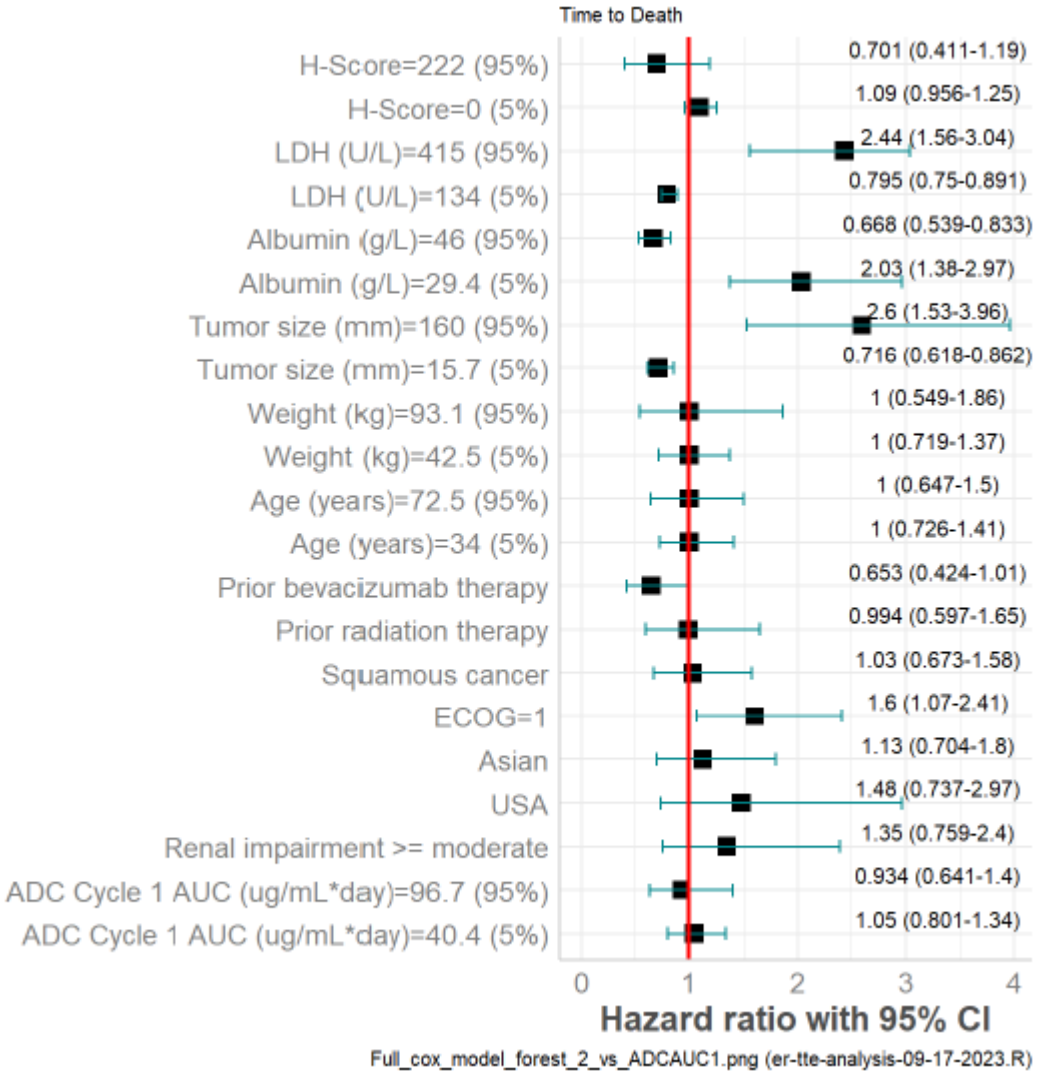


Figure 23 Cox PH Model for OS vs Cycle 1 ADC: Covariate Effects on the full model

Table 46 OS: Covariate Effects of Final CPH Models

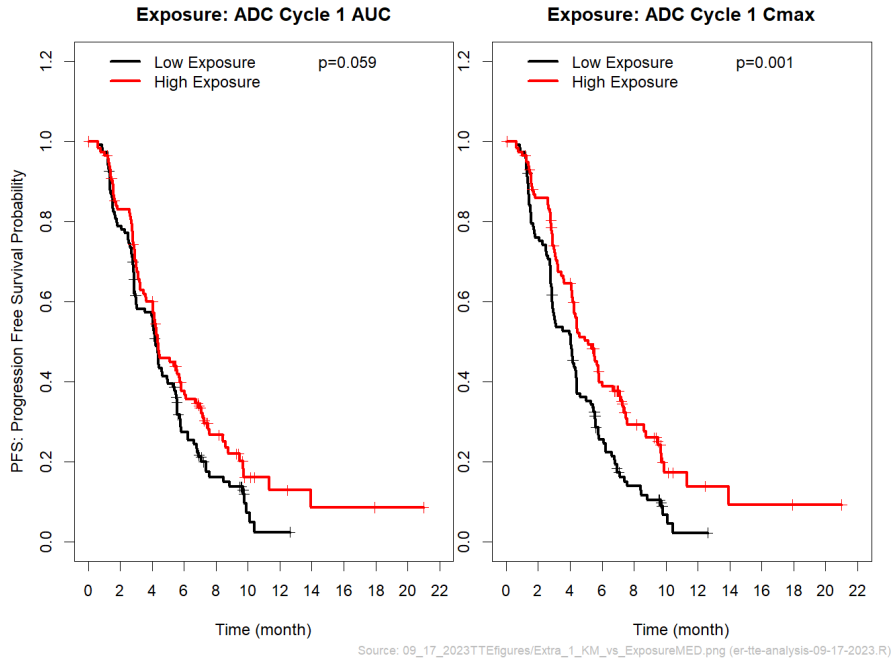
β = estimate for parameter; **SE**= standard error of β estimate; **RSE**= relative standard error of β estimate (%); **HR**= hazard ratio computed as exp(β); **HR95CI**= 95% confidence intervals on hazard ratio; **p-value**: significance level of β. Analyses associated with p <0.05 are denoted in boldred.

Exposure	β	SE	RSE	HR	95%CI	p-value	Model
ADC Cycle 1 AUC	0.008926	0.001989	22.28	1.009	1.005-1.013	<0.0005	SUMDIAM
	-0.07033	0.01817	25.83	0.9321	0.8995-0.9659	<0.0005	ALB
	0.00367	0.000768	20.92	1.004	1.002-1.005	<0.0005	LDH
ADC Cycle 1 C_{max}	0.0091	0.001979	21.74	1.009	1.005-1.013	<0.0005	SUMDIAM
	-0.07165	0.01813	25.3	0.9309	0.8984-0.9645	<0.0005	ALB
	0.003617	0.000765	21.15	1.004	1.002-1.005	<0.0005	LDH

Source: 09_17_2023_TTEsummaryTable.csv (er-tte-analysis_09_17_2023.R)

Secondary endpoints

PFS



Low exposure: ≤ median, High exposure > median. P value: p value of the log rank test comparing subjects with low and high exposure.

Figure 24 Kaplan Meier Plot by Exposure Groups: Time to Progression

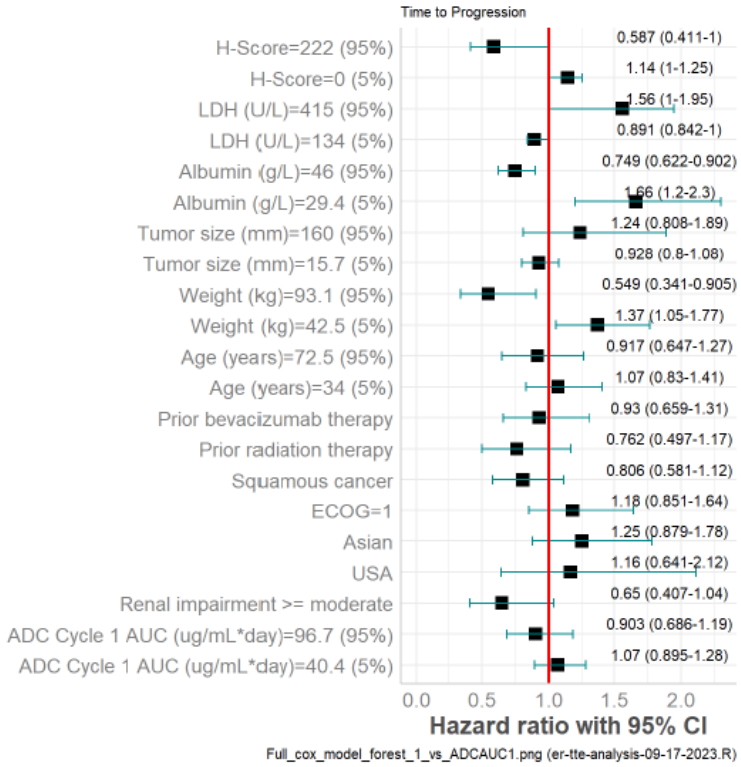


Figure 25 Cox PH Model for PFS vs Cycle 1 ADC AUC: Covariate Effects on the full model

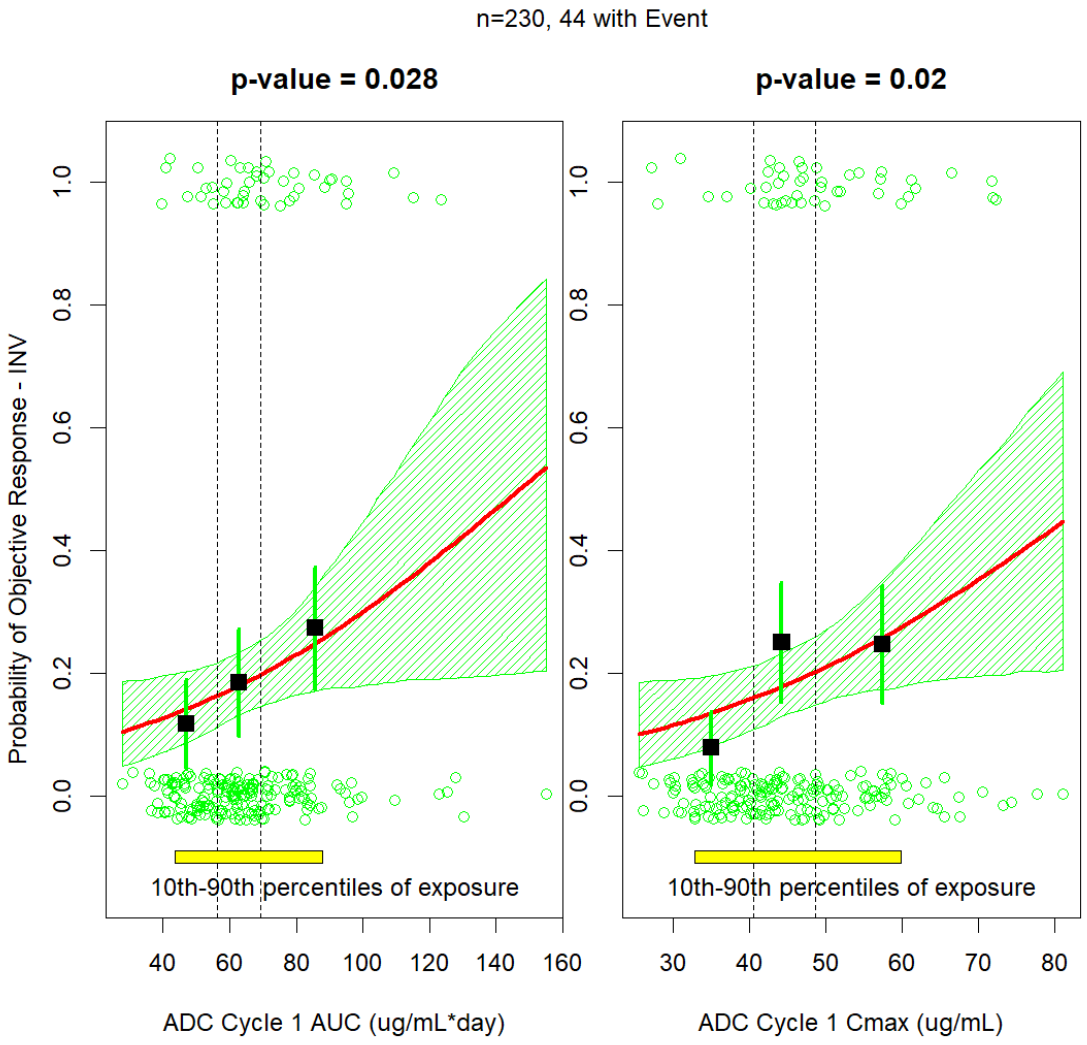
Table 47 PFS: Covariate Efefcts of Final CPH Models

β = estimate for parameter; SE= standard error of β estimate; RSE= relative standard error of β estimate (%); HR= hazard ratio computed as exp(β); HR95CI= 95% confidence intervals on hazard ratio; p-value: significance level of β. Analyses associated with p <0.05 are denoted in bold red.

Exposure	β	SE	RSE	HR	95%CI	p-value	Covariate
ADC Cycle 1 AUC	-0.04672	0.01419	30.36	0.9544	0.9282-0.9813	0.001	ALB
ADC Cycle 1 C_{max}	-0.04486	0.01415	31.55	0.9561	0.93-0.983	0.002	ALB

Source: 09_17_2023_TTEsummaryTable.csv (er-tte-analysis_09_17_2023.R)

ORR



Source: 09_17_2023ORRfigures/Extra_LogReg_ORR_vs_Exposure_ORR.png (er-tte-analysis-09-17-2023.R)

The red solid line and green shaded area represent the logistic regression model prediction and 95% CI of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0) vertically jittered for better visualisation. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% CI for these fractions. Dashed vertical lines show bounds of exposure tertiles. P value is provided by glm() function.

Figure 26: Logistic Regression for ORR Versus tisotumab vedotin Cycle 1 AUC and Cycle 1 C_{max} (Base Model)

Exposure-safety response

Exposure-safety analyses were conducted in 589 subjects who received tisotumab vedotin at 2.0 mg/kg Q3W. The analysis incorporated safety data pooled from 6 studies: GEN701 (Cohort Expansion part), GEN702 (Cohort Expansion part), GCT1015-06 (Cohort Expansion part), GCT1015-04, SGNTV-001 (Part A), and SGNTV-003 (Integrated Summary of Safety [ISS] Pool 2 Subset).

The specific objectives of the exposure safety analysis were:

• To describe the relationships of tisotumab vedotin and unconjugated MMAE exposure with probability of the following treatment emergent adverse events (TEAEs):

- any Grade ocular AEs;
- Grade 2 or higher (Grade 2+) ocular AEs;
- any Grade peripheral neuropathy;
- Grade 2+ peripheral neuropathy;
- any Grade bleeding AEs;
- Grade 2+ bleeding AEs;
- treatment related Grade 3 or higher (Grade 3+) TEAEs;
- treatment related dose modifications (dose reduction, dose interruption, dose discontinuation);
- all serious adverse events (SAEs) and treatment related SAEs;

• To determine the effect of tisotumab vedotin and unconjugated MMAE exposures on probability of AEs after accounting for selected key covariates.

Analyses of ISS Pool 2 Subset suggested that tisotumab vedotin Cycle 1 AUC (P=0.031 final model) and Cycle 1 Cmax (P=0.028) were predictors of the probability of treatment related TEAEs leading to dose discontinuations. Tisotumab vedotin Cycle 1 AUC (P=<0.0005 final model) and Cycle 1 Cmax (P=<0.0005 final model) were predictors of the probability of treatment related TEAEs leading to dose reductions and dose interruptions. In the same subject population, MMAE exposure was a predictor of the probability of treatment-related TEAEs leading to dose discontinuations (P=0.013 final model) (ER Report TRN-7394). Analyses of ISS Pool 2 Subset suggested that tisotumab vedotin Cycle 1 Cmax (P=0.020 final model) and Cycle 1 AUC (P=0.033 Final model) were predictors of the probability of treatment-related Grade 3 or higher AEs. In the same subject population, MMAE exposure was not a predictor of the probability of treatment-related Grade 3 or higher AEs.

The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. P-value is provided by *glm()* function.

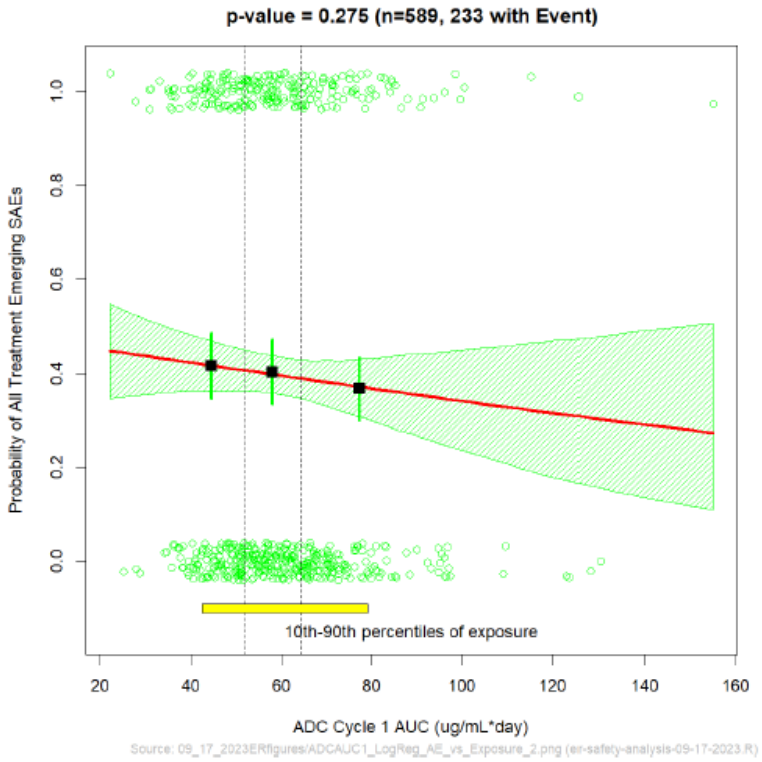


Figure 27 Logistic Regression for All SAEs vs ADC Cycle 1 AUC (Base Model)

The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. P-value is provided by *glm()* function.

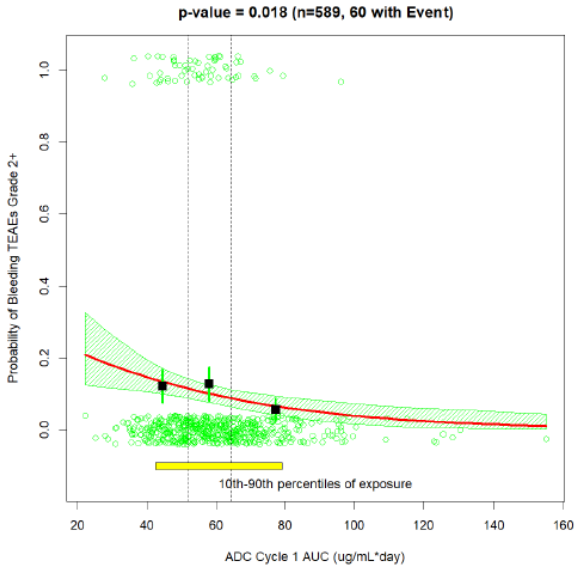


Figure 28 Logistic Regression for Grade 2+ Bleeding TEAE vs ADC Cycle 1 AUC (Base Model)

The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. P-value is provided by *glm()* function.

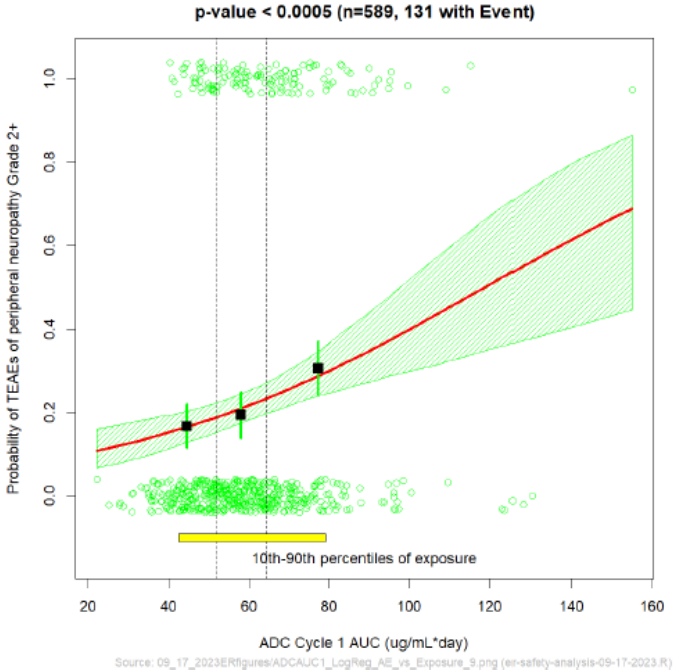
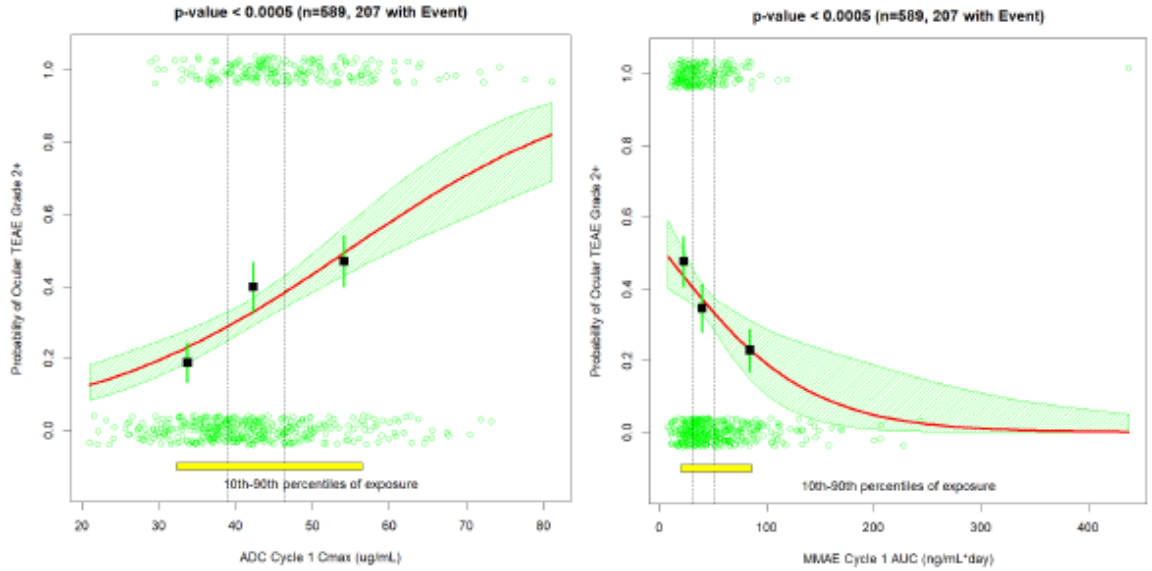


Figure 29 Logistic Regression for Grade 2+Peripheral neuropathy TEAE vs ADC Cycle 1 AUC (Base Model)



The red solid line and green shaded area represent the logistic regression model prediction and 95% CI of predictions. Points show exposure of individual subjects with events (p=1) and without events (p=0) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of subjects with events in each exposure tertile and 95% CI for these fractions. Dashed vertical lines show bounds of exposure tertiles. P value is provided by glm() function.

Figure 30 Logistic Regression for Grade 2 and Higher Ocular TAEs vs ADC Cmax and MMAE Exposure (Base Model)

2.4.3. Discussion on clinical pharmacology

Overall, bioanalytical methods appear robust and in good control. However, for SGNTV-003, not all TAB samples were analysed within established long-term stability of 213 days (Frontage, US). The missing stability data are recommended to be submitted as a post authorisation measure by February 2025 (**REC**).

Neutralizing Abs were detected in ADA positive samples from GCT1015-04 study, but not in SGNTV-003 study. This could be due to the poor sensitivity of the cell-based NaB assay used in SGNTV-003, however as ADAs do not appear to be a safety concern, this is acceptable.

Tisotumab vedotin PK was described by a complex four-compartment Pop PK model (Model 137). The model was developed on an earlier data set from two Phase 1/2 and two Phase 2 studies in subjects with various solid tumours known to express tissue factor including women with cervical cancer. Body weight had most impact on ADC exposure. Despite a weight proportional dosing, exposure increased with body weight. Dose capping was applied for patients with a body weight ≥100 kg at 200 mg. Model 137 was used to describe the exposure data from Phase 2 Study GCT1015-06 in Japanese subjects with solid tumours (n=23) and from the Phase 3 Study SGNTV-003 in women with cervical cancer (n=230) by external validation. No trend was observed in the goodness-of-fit plots (population conditional weighted residuals (CWRES) versus population predictions (PRED) and/or time) for study SGNTV-003. The amount of time points with CWRES values over 5 were below 2% of the total amount of time points for both ADC and MMAE, and retained in the data set. Three different drug products were used in the 6 studies included in the Pop PK analyses. There was no indication that drug product had influence on the PK or the model fit. SGNTV-003 and GCT1015 06 (Model 310mfs) were comparable. Therefore, even if Model 310mfs in principle is considered more comprehensive as data from the pivotal study have been included, Model 137 is considered fit to describe the PK of tisotumab vedotin in women with recurrent or metastatic cervical cancer and to inform the exposure-response models.

The presented mass balance study in patients was performed on a similar Antibody Drug Conjugated (ADC) with the same linker and cleavage mechanism as for tisotumab vedotin, namely brentuximab vedotin. This is acceptable. The mass balance study was performed with non-labeled MMAE and excreta were only collected for 1 week. As mass balance studies are normally not required for biologics, this is also acceptable.

The evaluation of the metabolism of MMAE is extensive and performed according to state of the art both *in vitro* and *in vivo*, although metabolite identification using radiolabelled MMAE in human plasma is missing. However, since MMAE has been used as cytotoxic payload in several other ADCs since 2013 resulting in similar levels of MMAE in plasma as for tisotumab vedotin (e.g. brentuximab vedotin and enfortumab vedotin) and that metabolite identification in human excreta did not identify metabolites of high abundance (>10% of MMAE), this deficiency is now considered redundant.

As expected for a monoclonal antibody, the dose normalised exposure ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$) for tisotumab vedotin and Total Antibody (TAB) increased with dose due to dose-related saturation of anticipated target mediated clearance (90% CI were above 1), whereas exposure of MMAE was linearly proportional to dose levels, (90% CI included 1). Dose proportionality was not evaluated at steady state. This is acceptable as no accumulation was observed. The POPPK model demonstrated that exposure to ADC and MMAE in cycle 1 and cycle 6 was highly correlated indicating that exposure to ADC and MMAE is not time- or cycle-dependent.

Volume of distribution and clearance of tisotumab vedotin and MMAE was estimated by population PK data obtained from the legacy analysis (model 137), which excluded the pivotal Phase 3 study (SGNTV-003) and additional Phase 1/2 study (GCT1015-06).

Inter-individual variability was low to moderate on AUC and C_{max} of ADC and TAB, however moderate to high on the same parameters of MMAE. No covariates were identified to cause this variability using POPPK modelling. Pharmacokinetic variability is sufficiently addressed.

The recommended dose of 2 mg/kg was considered MTD in the dose escalation study (GEN701), when administered once every 3 weeks (Q3W) and the dose of 2.2 mg/kg Q3W was too high. Synopsis Safety results reported the following: *On the 2.2 mg/kg dose level, 3 out of 6 subjects experienced 1 DLT each (diabetes mellitus type II, mucosal inflammation, and febrile neutropenia, all grade 3); thus, the MTD and RP2D were identified to be 2.0 mg/kg.*

Tisotumab vedotin is considered to have a narrow therapeutic index and any factors identified to increase exposure to the ADC and especially systemic exposure to free MMAE is described in the SmPC to prevent any unnecessary increase in exposure.

The results of drug-drug interaction studies suggest that co-administration with strong inhibitors of CYP3A4 will increase the exposure of free MMAE.

The results from effect of hepatic impairment on MMAE PK suggest that even mild hepatic impairment will increase the exposure to free MMAE. Patients with moderate and severe hepatic impairment were not included in the clinical studies. This is considered acceptable. Mild hepatic impairment had no impact on ADC exposure, however induced a 37% increase in C_{avg} of MMAE.

Overall, the incidence and severity of adverse events appear similar between patients with normal hepatic function and patients with mild hepatic impairment. However, in some cases, the incidence was higher in patients with hepatic impairment. Most importantly, none of these events led to treatment discontinuations in the patients with mild hepatic impairment. As a cautionary measure, a warning is included in section 4.4 of the SmPC of potential increase of exposure in patients with hepatic impairment.

The no-effect boundaries for effect of hepatic impairment and drug-drug interaction clinical studies can be defined as the inter-individual variability. This is acceptable due to the inherent toxicity of tisotumab vedotin and therefore anticipated narrow therapeutic index.

For what concern patient with renal impairment, based on enrolment criteria for the tisotumab vedotin clinical studies, enrolled subjects had either normal renal function, mild renal impairment, or moderate renal impairment. No dose adjustment is warranted for subjects with baseline mild or moderate renal impairment. The effect of severe renal impairment on the PK of tisotumab vedotin has not been assessed as these subjects were excluded from the clinical studies.

Tertiles of age were tested as a covariate in the POPPK model. No difference in C_{max} of ADC or MMAE was observed. This is supported.

MMAE is a substrate of P-gp, but not an inhibitor at clinically relevant plasma concentrations.

That MMAE is a substrate of P-gp is mentioned in section 4.5 of SmPC, however no recommendations on co-administration with P-gp inhibitors is provided. As the magnitude of increase in MMAE exposure was within interindividual variation with co-administration of brentuximab vedotin with ketoconazole, which is both and inhibitor of CYP3A4 and P-gp, it is agreed that for co-administration with a P-gp inhibitor alone with tisotumab vedotin, no dose recommendation is necessary.

MMAE was found to inhibit CYP3A4 in a time- and NADPH-dependent manner. Therefore, a clinical DDI study was performed with the CYP3A4 substrate midazolam and another vedotin ADC (brentuximab vedotin).

In vivo DDI studies on CYP3A4 for MMAE in this other ADC were conducted in cancer patients more than 10 years ago in support of the marketing authorisation of brentuximab vedotin (Han 2013).

Brentuximab vedotin had no impact on midazolam (CYP3A4 substrate) PK parameters including C_{max} and AUC. While mean C_{max} for MMAE is estimated to be approximately 6 ng/mL after infusion of tisotumab vedotin, it should however be noted that the range of C_{max} of MMAE is very large (1.29;65.7 ng/mL), much larger than for the ADC (24.5;74.3 ug/mL).

The geometric mean increases in exposure of MMAE, when co-administered with ketoconazole (CYP3A4 inhibitor) was 25% on C_{max} and 34% on AUC. SmPC, reflects this effect in broad terms and recommend that patients co-administered strong CYP3A4 inhibitors should be closely monitored for adverse reactions. No dose adjustment is recommended. As brentuximab vedotin showed time dependent clearance for MMAE, which is less pronounced for tisotumab vedotin and that the systemic concentration of MMAE is highly variable between patients, precise dosing recommendation on tisotumab vedotin co-administered with strong CYP3A4 inhibitors is difficult to estimate. Therefore, the wording as presented in section 4.5 of the SmPC is accepted.

As expected, the exposure of MMAE was reduced when tisotumab vedotin was co-administered with rifampin (a CYP3A4 inducer). As free MMAE has lost its target directing ability towards TF on cancer cells, free MMAE is more of a general systemic toxin inducing adverse effects in the patients. Hence, induction of CYP3A4 may even reduce systemic adverse events and as such no dose adjustment should be recommended in this case.

No primary pharmacology studies have been performed. The applicant has not defined any PD biomarkers. TF expression was retrospectively assessed and no correlation between TF expression and ORR was established. Therefore, no PD biomarkers are proposed for monitoring of the effect of treatment with tisotumab vedotin.

The c-QTc relation was explored by linear mixed-effects models of ΔQTcF versus observed concentrations of ADC or MMAE. Several paired PK-QT measurements were available at Cycle 1 following 2.0 mg/kg Q3W tisotumab vedotin (Study GCT1015-04). For MMAE, predicted concentration-ΔQTcF relationship indicates that QTcF is decreased with increasing concentrations, and does not signal for any QT prolongation effect. For ADC, the 95% confidence intervals do not exceed safety threshold of 10 msec for a clinically meaningful effect on QTc prolongation. The phenomenon of positive slope for ADC while unconjugated MMAE displays downward-trending slope has also been observed for other MMAE-containing ADCs (references to be included). The c-QTc relation was not explored at concentrations above those achieved following the projected posology and the linear modeling applied does not account for potential time-delay. Individual plots of Total Ab, ADC or MMAE concentrations versus QTcF change from baseline from Study GCT1015-04 showed no clear consistency across individual hysteresis plots, highlighting large variability in data between subjects. When focusing on time-matched QTc there is no consistent evidence of a time-delay. In Study GCT1015-04, 18 subjects experienced a post-baseline ΔQTcF >30 ms and 2 subjects experienced a post-baseline ΔQTcF >60 ms following the proposed 2.0 mg/kg Q3W dose regimen. No participant in either study with post-baseline ΔQTcF >30 ms experienced any clinically meaningful cardiac event. In study GCT1015-04, 1 participant experienced a >480 ms (none >500 ms). In study SGNTV-001 none of the participants experienced QTcF value >480 ms. Based on the integrated risk assessment (in line with ICH guideline Q&A E14/S7B) there is a low likelihood of a pro-arrhythmic effect for Tivdak, including negative non-clinical *in vitro* and *in vivo* results, negative phase 1 integrated exposure-response analyses and a clinical safety database with absence of signals in AEs including post-marketing data (please also refer to the non-clinical and clinical safety assessment). These data are in line with data from other MMAE-containing ADCs, for which no warnings are included in the SmPC. However, as the indication concerns a young female patient population and there remains some uncertainties regarding the linear mixed-

effects models and the exclusion of patients with cardiac disorders at baseline, QTc prolongation should be added as potential identified risk in the list of safety concerns. As a consequence, "cardiac arrhythmia" and "safety in patients with cardiac disorders" should be reported within PSUR.

The presence of ADA was detected in around 6% of patients across studies with RP2D of tisotumab vedotin. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited. Very low frequency of NAb was seen. Overall, this is reassuring and the risk of immunogenicity with treatment of tisotumab vedotin is *considered low.*

The exposure-response relationships were explored within the range of exposures associated with the 2.0 mg/kg Q3W tisotumab vedotin dosing regimen. Exposure metrics for the exposure-response modelling were AUC and Cmax at Cycle 1 and derived by Model 137. Relation of exposure to ORR and safety end-points were investigated using linear logistic regression models, while the relation of ADC exposure to probability of PFS, OS and DOR were explored by Kaplan-Meier plots and multivariate Cox proportional hazard models. Schoenfeld residual plots indicated the proportional hazard assumption was met for all analyses.

The exposure-efficacy relationships were assessed at one dose level, 2.0 mg/kg Q3W in 230 patients from the study SGNTV-003. A relationship between exposure and OS was found. Patients with higher ADC Cycle 1 Cmax had significantly longer OS. Similarly, a relationship between PFS and ORR and ADC Cycle 1 exposure was found. Kaplan-Meier plots showed that overall survival (OS) and progression-free survival (PFS) increased with an increase of tisotumab vedotin exposure. Covariate analysis indicated that OS significantly improved in patients with lower LDH, lower baseline tumour size, and higher albumin. However, OS was found to be independent of exposure. Similarly, base CPH models showed that after accounting for covariate effects (final model) the relationship between PFS and tisotumab vedotin exposure was not significant. The covariate analysis indicated that subjects with higher baseline albumin showed improved PFS, but this was independent of exposure. These results suggest potential confounding of the exposure-efficacy relationships by the subject characteristics included as covariates was observed throughout several efficacy endpoints. Furthermore, the limited dose range of only 2.0 mg/kg Q3W included in the analysis may lead to confounding of the exposure-response relationships with independent predictors of exposure and response, which further indicates that the relationship should be approached carefully.
The exposure-safety analyses were conducted on 589 patients at one dose level 2.0 mg/kg Q3W from 6 studies (ISS Pool 2 Subset). A relationship between exposure (cycle 1 ADC and/or Cmax) and the probability of treatmentrelated SAEs, Grade 3+ AEs, TEAEs leading to dose interruptions, dose reduction, or dose discontinuation, Grade 2+ and any grade ocular AEs, as well as Grade 2+ and any grade peripheral neuropathy was found. The increase of MMAE exposure only increased the probability of TEAEs or SAEs and even decreased the probability of other adverse events. These opposite trends were previously seen in other MMAE-containing ADCs.

2.4.4. Conclusions on clinical pharmacology

The pharmacokinetics of tisotumab vedotin appear sufficiently evaluated experimentally *in vitro* and *in vivo*. The clinical pharmacology package is considered acceptable.

2.4.5. Clinical efficacy

2.4.5.1. Dose response studies

The GEN701 study established the recommended dose of tisotumab vedotin administered by IV infusion at 2.0 mg/kg Q3W. The dose escalation part in GEN701 applied a standard 3 (+3) design to evaluate tisotumab vedotin at doses ranging from 0.3 to 2.6 mg/kg. Based on the results of this study, 2.0 mg/kg was identified as the recommended phase 2 dose (RP2D). Tisotumab vedotin 2.0 mg/kg Q3W was further evaluated in the phase 2 GCT1015-04 study. Results from the GCT1015 04 study demonstrated clinically meaningful efficacy in subjects with r/mCC with a manageable safety profile, which supported 2.0 mg/kg Q3W as the recommended dose in the US product labeling. Confirmed ORR assessed by Independent Review Committee (IRC) was 23.8% (95% CI: 15.9, 33.3), including 7 (6.9%) complete responses (CRs) and 17 (16.8%) partial responses (PRs). See Clinical Pharmacology Section.

2.4.5.2. Main study

Study SGNTV-003/ innovaTV 301 Study

SGNTV-003 (innovaTV 301), is a phase 3, randomised, open-label study comparing tisotumab vedotin to chemotherapy in subjects with 2L or third line (3L) recurrent or metastatic cervical cancer (r/mCC). Eligible subjects were randomised 1:1 to either tisotumab vedotin 2.0 mg/kg Q3W or 1 out of 5 chemotherapy choices (topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed). No crossover between the 2 treatment arms was permitted.

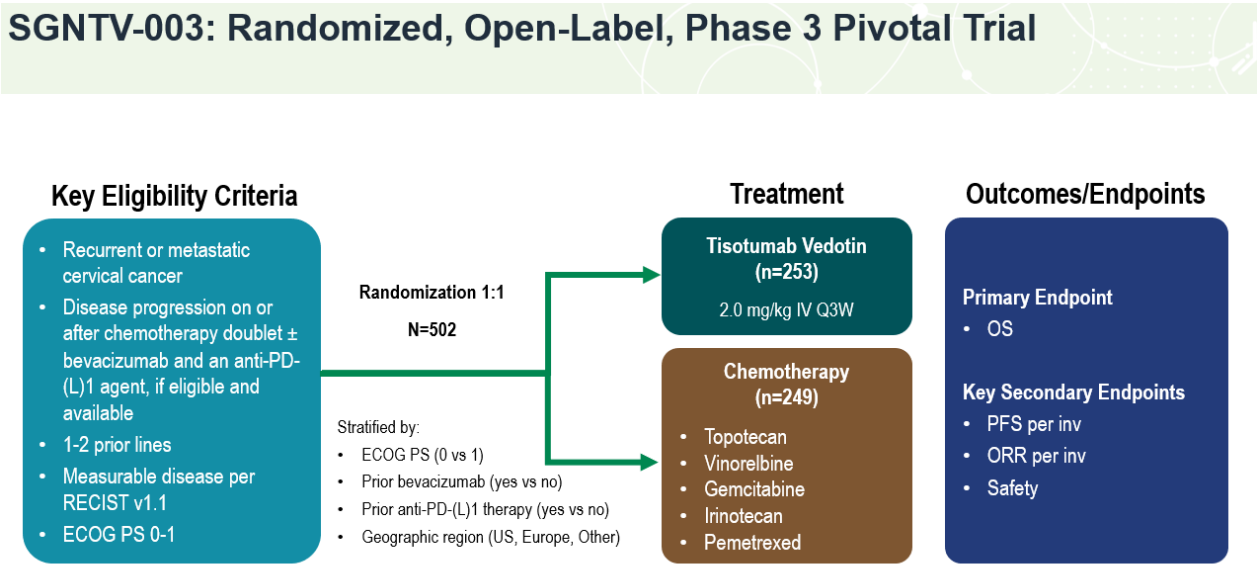


Figure 31: Study schema

Methods

- **Study Participants**

Main Inclusion criteria according to the latest protocol version:

1. Age ≥18 years, or considered an adult by local regulations, at time of consent.

2. Signed an informed consent form indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study prior to any other study-related assessments or procedures.

3. Had r/mCC with squamous cell, adenocarcinoma, or adenosquamous histology, and:

- Had 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 was not a standard of care therapy or the subject was ineligible for such treatment according to local standards, prior treatment with bevacizumab and/or anti-PD-(L)1 agent was not required.
- Had received 1 or 2 prior systemic therapy regimens for r/mCC. Chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, should not have been counted as a systemic therapy regimen. Single agent therapy with an anti-PD-(L)1 agent for r/mCC was counted.
- Was 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 minimum of 1 non-nodal lesion ≥10 mm in the longest diameter from a non-irradiated area. If target lesion(s) were located within previously irradiated area only, the subject was enrolled only if there had been demonstrated progression in the "in field" lesion and upon approval of the sponsor's medical monitor.
  OR
- Lymph node lesion ≥15 mm in the shortest diameter from a non-irradiated area.

5. Had demonstrated acceptable screening laboratory values

6. Had ECOG performance status of 0 or 1 prior to randomisation.

Main exclusion criteria:

1. Had primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned in inclusion criterion 3.

2. Had clinically significant bleeding issues or risks:

- Known past or current coagulation defects leading to an increased risk of bleeding
- Diffuse alveolar hemorrhage from vasculitis
- Known bleeding diathesis
- Ongoing major bleeding (ie, subject requires a transfusion of >2 platelet concentrates within 14 days of the first dose of study treatment)
- Trauma with increased risk of life-threatening bleeding
- History of severe head trauma or intracranial surgery within 8 weeks of study entry.

3. Had cardiovascular issues or risks:

- Clinically significant cardiac disease, including unstable angina or acute myocardial infarction, 6 months prior to screening
- Any medical history of congestive heart failure (Grade III or IV as classified by the New York Heart Association)
- Any medical history of decreased cardiac ejection fraction of <45%
- A marked baseline prolongation of QT/QT corrected (QTc) interval (eg, repeated demonstration of a QTc interval >450 msec)
- A complete left bundle branch block (defined as a QRS interval ≥120 msec in left bundle branch block form) or an incomplete left bundle branch block

4. Central nervous system: any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening was 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 (SJS) or toxic epidermal necrolysis, mucus pemphigoid, and subjects with penetrating ocular transplants were ineligible. Cataracts alone was not an exclusion criterion.

6. Other cancer: known past or current malignancy other than inclusion diagnosis. Exceptions were malignancies with a negligible risk of metastasis or death (eg, 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 were allowed if the following criteria were met: definitive therapy (eg, surgery or stereotactic brain radiotherapy) had been completed >8 weeks before the first dose of study treatment; no evidence of clinical or radiologic progression of the brain metastases; subjects had completed perioperative corticosteroid therapy or steroid taper. NOTE: Chronic steroid therapy was acceptable provided that the dose was 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. Subjects must have recovered adequately from the toxicity or complications from the intervention prior to starting study treatment. Subjects who have planned major surgery during the treatment period were excluded from the study.

9. Peripheral neuropathy ≥Grade 2.

10. Prior anti-cancer therapy:

- Any prior treatment with monomethyl auristatin E-derived drugs.
- Radiotherapy within 21 days prior to the first administration of study treatment. Subjects must have recovered from all clinically significant radiation-related toxicities. At least 42 days were to have elapsed from the last administration of chemo radiotherapy.
- Small molecules, chemotherapy, immunotherapy, or monoclonal antibodies within 28 days prior to the first administration of study treatment.
- Current participation in or had 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:

- Ongoing significant, uncontrolled medical condition.
- Clinically significant active viral, bacterial, or fungal infection requiring intravenous (IV) or oral treatment with antimicrobial therapy ending <7 days prior to first study treatment administration.
- Clinically relevant bilateral hydronephrosis which could not be alleviated by ureteral stents or percutaneous drainage.
- Subjects with clinical symptoms or signs of gastrointestinal obstruction and who required parenteral hydration or nutrition at the time of the first dose of study treatment.

12. Had 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 was required, unless mandated by local health authorities. Exceptions included latent or controlled HIV infection.

13. Had a diagnosis of immunodeficiency or was 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. Was pregnant or intended to conceive children within 6 months of ending study treatment.

15. Was breast feeding and could not 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 subject (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. Had known psychiatric or substance abuse disorders that would have interfered with cooperating with the requirements of the study.

Treatments

Subjects were randomised to receive either tisotumab vedotin or chemotherapy. No crossover between treatment arms was permitted.

Tisotumab vedotin 2.0 mg/kg was administered as an IV infusion on Day 1 of each 3-week treatment cycle (21 days).

Chemotherapy options were:

- 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 participants who do not tolerate the protocol-specified dosing schedule, dose reductions were permitted in order to allow the participant to continue treatment with tisotumab vedotin. Dose modifications guidelines for tisotumab vedotin were according the following scheme:

Table 48 tisotumab vedotin Dose Modification Scheme-Study SGNTV-003

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.

Dose modifications for **the chemotherapy arm** were performed as per local labelling or institutional guidelines, additionally recommendations guidelines were provided in the study.

Dose delays for tisotumab vedotin were allowed. For any dose delay due to AEs, dosing with tisotumab vedotin could be resumed immediately after the AE has improved as indicated in the dose modification guidance. 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.

Tisotumab vedotin treatment was to be **permanently discontinued** in case the participant fulfilled any of the below criteria:

- 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
- 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

Treatment discontinuation due to AEs for the chemotherapy administered in the chemotherapy arm was done per investigator's discretion regarding local labelling or institutional guidelines.

Objectives and corresponding endpoints

Primary Objective and endpoint

Demonstrate improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in subjects with second- or third-line (2L-3L) cervical cancer

The primary endpoint of this study was OS. OS was defined as the time from the date of randomisation to the date of death from any cause.

OS = Date of death or Censoring date – Date of randomisation +1.

H0: OS of the TV arm had no difference from that of the control arm.

Kaplan-Meier curves and estimates of the median OS time were to be provided for each arm with the two-sided 95% CI using the complementary log-log transformation method KM estimates of the 25th and 75th percentiles of the OS time and the observed minimum and maximum OS time were also to be reported. In addition, the estimated probability of OS at landmark time points (for example, every 3 months) and their 95% CIs were also to be reported. The hazard ratio and 95% CI were to be estimated using a stratified Cox proportional hazards regression model controlling for the randomisation stratification factors, except for region.

Hypothesis testing were to be performed on the primary endpoint of OS and the 2-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. The endpoints were tested in the hierarchical order as follows: OS first, then PFS, and finally ORR.

Secondary objectives and endpoints

Secondary	
• Assess improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with 2L-3L r/mCC	• 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 r/mCC	• 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 r/mCC	• 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)	• European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) • EORTC Quality of Life Questionnaire cervical cancer module (QLQ-CX24) • EuroQol-5 dimension (EQ-5D; consisting of EQ-5D-5 level [5L] descriptive system and EQ visual analog scale [VAS])
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 tumor tissue in relation to efficacy endpoints
• Evaluate the pharmacokinetics (PK) and immunogenicity of tisotumab vedotin	• PK concentrations and antidrug antibodies (ADAs) associated with tisotumab vedotin

PFS

PFS was defined as the time from the date of randomisation to the first documented disease progression (as assessed by investigator per RECIST v1.1) or death from any cause, whichever occurred first.

Specifically, PFS was derived as:

PFS Event Date (Date of first documented PD or death) or Censoring date–Date of randomisation + 1

PFS were to 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 were to be censored at the date of the last adequate tumour assessment prior to data cut-off date or the start of new anti-cancer therapy. Participants with disease progression or death that occurred after 2 or more missed scans would have been censored at the last adequate tumour assessment prior to the missed scans. If there was no documented disease progression or death, the subject were censored at the date of the last tumour assessment where the disease was classified as complete response (CR), partial response (PR), stable disease (SD), or non-CR/non-PD. Participants without post-baseline scan data would have been censored at the day of randomisation.

Table 49 Censoring Scheme for primary Analysis of PFS per RECIST v1.1 per investigator

Scenario	Progression/Censor Date	Outcome
No post-baseline tumor assessments[a]	Date of randomization	Censored
No documented disease progression or death	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censored
New anti-cancer treatment (systemic, radiation, or surgery) started before PD or death observed	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of new anti-cancer treatment	Censored
Progressive disease (PD)	Date of PD	Event
Death before first PD assessment[b]	Date of death	Event
Death or progression right after two or more consecutive missed tumor assessments	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD prior to the missed visits	Censored

[a] Censoring date will be date of randomization when 1) no post-baseline tumor assessment and no death, or 2) no post-baseline tumor assessment and with death after a prolonged duration (eg., after the planned 2nd response assessment date);
[b] Patient with no post-baseline tumor assessment and with death within a prolonged duration (eg., before the planned 2nd response assessment date) will be counted as a death event.

ORR

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

ORR was to be analyzed using a Cochran-Mantel-Haenszel chi-squared test. The common odds ratio across strata was to 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 tumour assessments were to be considered to be non-responders.

Other secondary endpoints

DOR

DOR was defined as the time from the date of the first confirmed objective response (CR or PR that is subsequently confirmed) to the date of the first documented PD per RECIST v1.1 or death from any cause, whichever occurred first. The same derivation of PD date and censoring rules as described in Table 1 for primary PFS analysis were to be applied for DOR.

Analysis of DOR would include the subgroup of subjects in the ITT analysis set who achieve a confirmed CR or confirmed PR based on investigator assessment. KM curves and the estimates of median DOR with corresponding 95% CIs for each treatment arm were to be provided with the two-sided 95% CI using the complementary log-log transformation method.

TTR

TTR was defined as the time from the randomisation date to the date of the first confirmed objective response (CR or PR that is subsequently confirmed).

Analysis of TTR would include the subgroup of subjects in the ITT analysis set who achieve a confirmed CR or confirmed PR based on investigator assessment. TTR would be summarised using the descriptive statistics.

Sample size

Approximately 482 subjects were to be randomised in a 1:1 ratio to one of the 2 study arms. This sample size was 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 ≠ 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 interim analysis (IA) at approximately 75% (252) of the total number of OS events using the Lan deMets (O'Brien Fleming) boundary

• accrual duration of approximately 23 months with at least 12 months of follow-up

• 1:1 randomisation ratio

The IA and final analysis (FA) on OS were estimated to occur at approximately 27 and 35 months after the first subject is randomised into the study.

At the OS IA and FA, it was estimated that the number of PFS events would have been approximately 413 and 457, respectively, which would 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 was estimated that all 482 subjects would have been fully randomised into the study, based on the assumed accrual, and have at least 2 post-baseline scans at the OS IA and FA timings.

This would provide 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.

Randomisation and Blinding (masking)

This is an open-label study. In order to maintain study integrity, analyses or summaries by randomised treatment or actual treatment assignment were limited and documented while the study was ongoing and before the database lock for primary analyses.

The study had 2 treatment arms, and randomisation occurred centrally using an RTSM system. Subjects were assigned randomly in a 1:1 ratio to either tisotumab vedotin or chemotherapy. Chemotherapy was assigned and recorded for each subject prior to randomisation. Additionally, the proportion of subjects who had not received prior bevacizumab in combination with chemotherapy as 1L treatment was capped at 50%. Randomisation was 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

Blinding of the study was not operationally feasible due to the substantial differences in toxicity profile, cycle lengths, treatment administration, and required pre-medications.

Results of the planned OS, PFS, and ORR interim analyses were to be provided to the IDMC by an external independent vendor.

Statistical methods

ANALYSIS SETS

Intent-to-Treat (ITT) Analysis Set

The intent-to-treat (ITT) analysis set would include all subjects who were randomised on or before the date of last-patient-in (LPI) in the global study. Subjects would have been included in the treatment group assigned at randomisation regardless of any actual treatment received.

Safety Analysis Set

The safety analysis set would include all subjects who were randomised on or before the date of LPI in the global study and received any amount of study treatment. Subjects were to be analyzed according to the actual treatment received. Subjects who received any dose of tisotumab vedotin would have been included in the TV treatment group in the Safety Analysis Set.

Patient Reported Outcomes Full Analysis Set (PRO FAS)

The PRO FAS would include all subjects who were randomised on or before the date of LPI in the global study and have received any amount of study treatment and have completed baseline and at least one post-baseline PRO assessment. The PRO FAS was to be used for PRO analyses.

Efficacy analyses for the primary endpoint

Primary analyses for OS

The null hypothesis for the primary endpoint was that the OS of the TV arm had no difference from that of the control arm. To test this hypothesis, a stratified log-rank test comparing two arms in the ITT analysis set would have been conducted controlling for the randomisation stratification factors [i.e., ECOG status (0 vs. 1), prior bevacizumab administration (yes vs. no) and prior anti-PD-L1/PD-1 administration (yes vs. no)].

Kaplan-Meier curves and estimates of the median OS time were to be provided for each arm with the two-sided 95% CI using the complementary log-log transformation method KM estimates of the 25th and 75th percentiles of the OS time and the observed minimum and maximum OS time would had also be reported. In addition, the estimated probability of OS at landmark time points (for example, every 3 months) and their 95% CIs would also be reported. The hazard ratio and 95% CI would have been estimated using a stratified Cox proportional hazards regression model controlling for the randomisation stratification factors, except for region.

Hypothesis testing would have been 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. The Lan- DeMets O'Brien-Fleming approximation spending function would have been used to obtain the efficacy boundaries at the IA and final OS analyses.

Proportional hazards (PH) assumption for treatment arms would have been examined with the following approaches:

1. Plot of 'log-negative-log' of the KM estimator of the survival function versus log(time) by treatment arm. Parallel curves with constant distance over time indicate the PH assumption is met.

2. Plot of Schoenfeld residuals for the treatment variable versus time. With proportional hazards, the LOESS curve should be parallel to the x-axis. Residuals that do not show any trend indicate that the PH assumption is met.

Sensitivity Analyses for OS

1. *Unstratified Analysis***:** OS analysis by unstratified log-rank test to compare the treatment arms. Additionally, an unstratified Cox regression model will be used to estimate the hazard ratio and the corresponding 95% CI for the treatment effect. The same censoring method as for the primary analysis of OS will be used.

2. *Mis-stratification:* In the case of > 5% inconsistency in stratification factors between RTSM and eCRF, the stratification factors collected at eCRF was to be used as strata in both stratified log-rank test and stratified Cox proportional hazards regression model.

3. *Initiation of Subsequent Cancer-related Therapy:* Start subsequent cancer-related therapy was likely to bias the analyses of OS, more specifically, could underestimate OS comparison when the distribution of subsequent therapies was imbalanced between 2 arms. To reduce such bias, the following OS sensitivity analysis could be planned: Inverse probability of censoring weights (IPCW) method. Subjects who took subsequent therapy were to be censored at the time of sequent cancer-related therapy, but subjects were to be weighted according to their probability to take subsequent therapy.

4. *Non-proportional hazard***:** In the case that the PH assumption was violated, OS could be analyzed based on a restricted mean survival time (RMST) up to τ and τ will be the minimum of (largest observed OS event time for the TV arm, largest observed OS event time for the control arm). Comparison of RMST between treatment arms was to be performed using the KM curve-based test. RMST for each treatment arm and difference in RMST between the treatment arms were to be provided with the corresponding 95% CIs.

Analyses for the key secondary efficacy endpoints

Primary and sensitivity analyses for PFS

The two arms were to be compared for PFS using a stratified log-rank test controlling for the stratification factors in ITT population. Kaplan-Meier curves and estimates of the median PFS time would have been provided for each arm with the two-sided 95% CI using the complementary log-log transformation method. KM estimates of the 25th and 75th percentiles of the PFS time and the observed minimum and maximum PFS time would also be reported. In addition, the estimated probability of PFS at landmark time points (for example, every 3 months) would have been reported. The hazard ratio and 95% CI would have been estimated using a stratified Cox proportional hazards regression model controlling for the randomisation stratification factors.

Hypothesis testing starts with OS and wold only proceed to the hypothesis testing on the next endpoint, PFS, when the efficacy boundary was crossed for OS at the first time (IA or FA).

PH assumption would have been examined using the same method as described for OS.

Several sensitivity Analyses were planned for PFS:

1. *New Subsequent cancer-related therapy before PD/death:* For subjects who received subsequent cancer-related therapy before PD or death, two sensitivity analyses would have been performed:

• Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason.

• Consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as an event.

2. *Missing Tumour Assessments:* To explore the potential impact of missing tumour assessments on PFS, subjects who missed two or more consecutive scheduled assessments before death or PD were to be considered to have had an event, with the earlier date of death or progression as event date.

3. *Mis-stratification:* In the case of >5% inconsistency in stratification factors between RTSM and eCRF, the stratification factors collected at eCRF would have been used as strata in both stratified log-rank test and stratified Cox proportional hazards regression model.

Primary and sensitivity analyses for ORR

Confirmed ORR per investigator was defined as the proportion of subjects with a confirmed CR or PR per RECIST v.1.1 per assessment by investigator. Only response assessments before the first documented PD or new anti-cancer therapies would have been considered. For a response to be considered as confirmed, the subsequent response needed to be at least 4 weeks after the initial response. The minimum criteria for SD duration were defined as ≥ 5 weeks after the date of randomisation.

The primary analysis of confirmed ORR was to be conducted for subjects in the ITT analysis set with measurable disease at baseline. The ORR and its 2-sided 95% exact CI were calculated for each treatment arm using the Clopper-Pearson method.

Comparison in confirmed ORR between treatment arms were tobe performed using a Cochran- Mantel-Haenszel (CMH) chi-squared test stratifying for the stratification factors. The common odds ratio across strata were to be estimated with its 95% CI and 2-sided p-value for testing of superiority of TV over chemotherapy.

The hypothesis testing on confirmed ORR would only occurredafter the efficacy boundary was crossed for PFS.

One sensitivity Analyses was planned for Confirmed ORR:

*Mis-stratification***:** In the case of >5% inconsistency in stratification factors between RTSM and eCRF, the stratification factors collected at eCRF will be used as strata in the CMH test.

Analyses for the other secondary efficacy endpoints

Duration of Response (DOR)

DOR wasdefined as the time from the date of the first confirmed objective response (CR or PR that is subsequently confirmed) to the date of the first documented PD per RECIST v1.1 or death from any cause, whichever occurred first. The same derivation of PD date and censoring rules as described in

Analysis of DOR would have included the subgroup of subjects in the ITT analysis set who achieve a confirmed CR or confirmed PR based on investigator assessment. KM curves and the estimates of median DOR with corresponding 95% CIs for each treatment arm were to be provided with the two-sided 95% CI using the complementary log-log transformation method.

Time to Response (TTR)

TTR was defined as the time from the randomisation date to the date of the first confirmed objective response (CR or PR that was subsequently confirmed).

Analysis of TTR would have included the subgroup of subjects in the ITT analysis set who achieve a confirmed CR or confirmed PR based on investigator assessment. TTR was to be summarised using the descriptive statistics.

Handling of Withdrawals, Discontinuations, and Missing Data

Subjects who did not have at least 2 (initial response and confirmation scan) post-baseline response assessments were to be counted as non-responders for analysis of the confirmed ORR.

With the following exceptions, missing data were not imputed.

- Missing AE dates were imputed for the purpose of calculating duration of events and determining the treatment-emergent status. Missing disease diagnosis date was imputed for the purpose of calculating the time from diagnosis to date of randomisation or date of first dose.
- Missing subsequent cancer-related therapy start date was imputed for the purpose of deriving the time-to-event endpoints as applicable.
- For prior therapies start dates, if month and year were present and only day was missing, the day was imputed as the first day of the month. If month or year was missing, no imputation was performed.
- For prior therapies end dates, if month and year were present and only day was missing, the day was imputed as the last day of the month or 21 days before the first dose of study drug, whichever was earlier. If the imputed end date was earlier than start dates, the end day was imputed as the day after the start date. If month or year was missing, no imputation was performed.

Error probabilities, adjustment for multiplicity and interim analyses

Hypothesis testing was to 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.

The endpoints were tested in the hierarchical order as follows: OS first, then PFS, and finally ORR. Hypothesis testing starts with OS and would have only proceeded to the hypothesis testing on the next endpoint, PFS, when the efficacy boundary was crossed for OS at the first time (IA or FA). Similarly, the hypothesis testing on ORR would have only occurred after the efficacy boundary is crossed for PFS.

For OS, the Lan DeMets (O'Brien-Fleming) spending function was to be used. With approximately 252 and 336 events estimated to occur at the IA and FA respectively, the OS was to 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 was tol be used. With approximately 413 and 457 events estimated to occur at the OS IA and FA respectively, the PFS was to 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 was estimated that all 482 subjects would have to be fully randomised into the study and had the opportunity to have at least two post-baseline scans by the OS IA at 27 months. The ORR was to be tested at 2-sided 5% level corresponding to an odds ratio boundary of 1.67.

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

Changes from protocol-specified analyses

Table 50 Changes from the Original SAP

Section# and Name	Description of Change
Section 5 Analysis set	Clarified the definition of the analysis sets
Section 6.4 Data transformation and derivation	Clarified study day definition and clarified PD backdating rule for new lesion as specified in RECIST 1.1
Section 6.5 Handling of dropouts and missing data	Removed sentence regarding PK measurements
Section 6.8 Examination of subgroups	Updated list of subgroups
Section 7.2 Demographic and baseline characteristics	Updated list of disease specific characteristics
Section 7.4 Treatment administration	Clarified duration of treatment and IDI
Section 7.5.1 Primary endpoint	Clarified on the OS censoring
Section 7.5.2 Key secondary endpoints	Clarified a minimum required length for SD as a best overall response
Section 7.6.1 Adverse events	Clarified on algorithm to compute date of improvement Updated summary of TEAE presentations Clarified dose modification definition Removed a sentence that is not applicable to AESI
Section 7.7.1 Pharmacokinetics	Updated the analysis summary

Results

- **Participant flow**

Of 660 patients who signed the informed consent, 158 (23%) were screening failures. Not meeting the eligibility criteria (85.4%) and withdrawn consent (8.9%) were the most frequent reasons of screening failures. 502 patients were randomised with 253 allocated to tisotumab vedotin and 249 to chemotherapy arm.

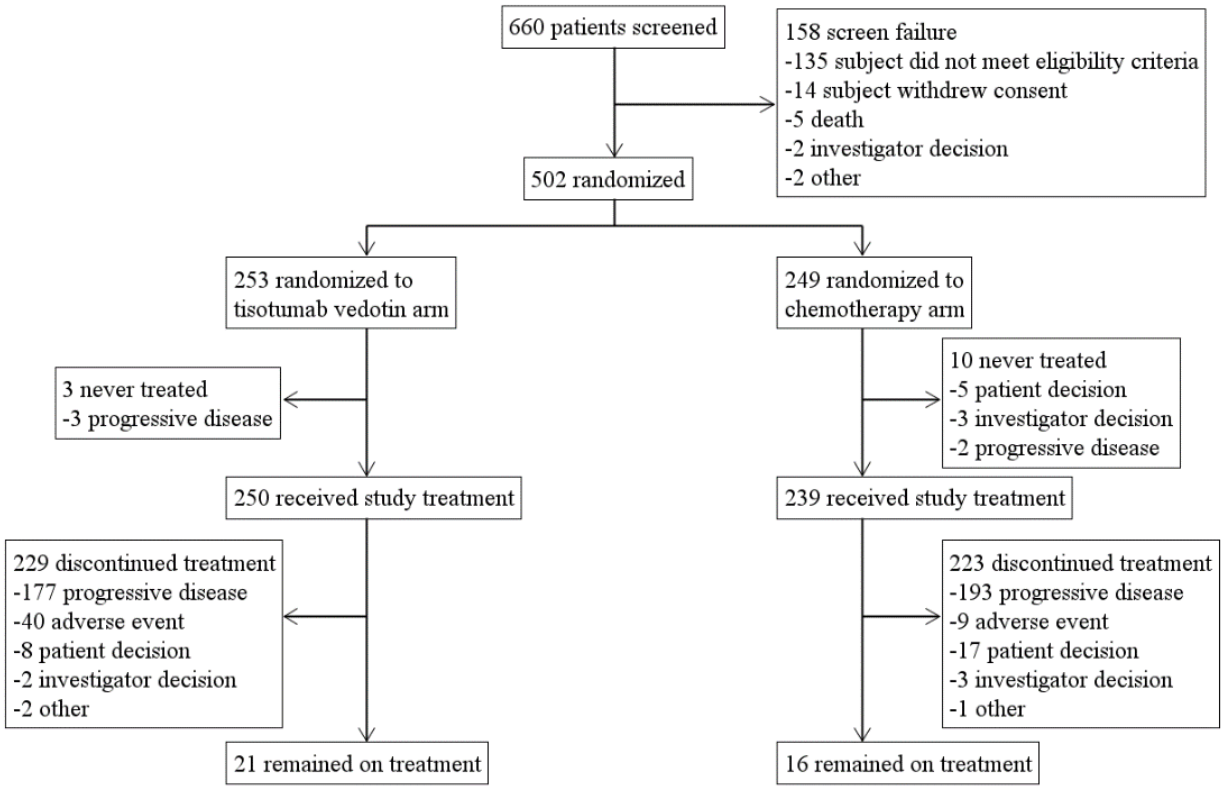


Figure 32 Participant Flow SGNTV-003 All Screened Subjects

Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Recruitment

The study SGNTV-003 is a global study, which was conducted at 168 sites in 25 countries: Argentina, Austria, Belgium, Brazil, Canada, China, Czech Republic, Finland, France, Germany, Hungary, Italy, Japan, Mexico, Netherlands, Norway, Peru, Poland, Singapore, South Korea, Spain, Sweden, Taiwan, UK and US.

First subject enrolled: 09-Mar-2021

Data cutoff date for primary analysis: 24-Jul-2023

Study status: ongoing

At the DCO (24-Jul-2023) median follow-up time from randomisation to death was 10.8 months (95% CI: 10.3, 11.6) for the total study population.

Conduct of the study

The original version of the protocol was approved on 17-Sep-2020. The protocol was amended 3 times during the course of the study.

Table 51 Summary of protocol amendment for Protocol SGNTV-003

Version	Date	Key changes
Original protocol	17-Sep-2020	---
Amendment 1	23-Nov-2020	Pemetrexed added as an option for chemotherapy arm Duration of tisotumab vedotin dose delay due to toxicity changed from 12 weeks to 6 weeks before treatment is discontinued Added lifestyle recommendations to avoid contributing factors to the development of dry eye Pregnancy test results no longer excepted from reporting to central laboratory
Amendment 2	20-Aug-2021	Randomization window changed from within ≤3 days of C1D1 to within ≤7 days Steroid eye drops are to be administered on Day -1 of each cycle Premedication for chemotherapy at C1D1 removed Additional statements added on known and potential risks Inclusion criterion for minimum age modified Calculated eGFR (MDRD formula) threshold changed from >50 mL/min/1.73m^2 to ≥50 mL/min/1.73m^2 Inclusion criterion 12 removed Permanent discontinuation of tisotumab vedotin added as a dose modification rule for bleeding events and elevated liver parameters of grade 4 severity HbA1C removed from table of laboratory assessments
Amendment 3	06-Apr-2022	eGFR to be collected within 7 days of C1D1 instead of within 28 days Radiology assessments to be performed at EOT, with exception for previous tumor imaging obtained within 4 weeks Health-related quality of life assessments to be collected "<7 days" of C1D1 instead of "≤ 7 days". Plasma protein biomarkers removed Clarified starting dose for topotecan and irinotecan Prior anti-PD-(L)1 therapy added Exclusion #6 language revised to focus on prognosis/survival Exclusion #12 amended to include exceptions for latent or controlled HIV infection. Herbal medicines removed Safety reporting period for all AEs amended to 30 days after the last study treatment Follow-up duration extended to up to 6 months of age for the child Circulating tissue factor assay removed from the biomarker analysis

Table 52. Summary of Subjects with Protocol Deviations

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy [a] (N=249) n (%)	Total (N=502) n (%)
Subjects with any protocol deviations	245 (96.8)	230 (92.4)	475 (94.6)
Important protocol deviations[b]	21 (8.3)	23 (9.2)	44 (8.8)

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy [a] (N=249) n (%)	Total (N=502) n (%)
Minor protocol deviations	245 (96.8)	229 (92.0)	474 (94.4)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Important deviations are Study Protocol Violations which meet pre-defined criteria impacting completeness, accuracy, and/or reliability of the study data and have the potential for a significant effect on a subject's rights, safety, or well-being. All other protocol deviations are considered minor.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Table 53 Important Protocol Deviations

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy[a] (N=249) n (%)	Total (N=502) n (%)
Any important protocol deviation[b]	21 (8.3)	23 (9.2)	44 (8.8)
Reason for important protocol deviation[c]			
Stratification error	12 (4.7)	17 (6.8)	29 (5.8)
Inclusion criterion	4 (1.6)	5 (2.0)	9 (1.8)
Investigational product administration	2 (0.8)	1 (0.4)	3 (0.6)
Study conduct	2 (0.8)	0	2 (0.4)
Exclusion criteria	1 (0.4)	0	1 (0.2)
Informed consent	1 (0.4)	0	1 (0.2)

a. The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

b. Important deviations are Study Protocol Violations which meet pre-defined criteria impacting completeness, accuracy, and/or reliability of the study data and have the potential for a significant effect on a subject's rights, safety, or well-being.

c. Subjects may be counted in more than 1 category.

Baseline data

Table 54 Demographics Characteristic Study SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)	Total (N=502)
Age (year)			
n	253	249	502
Mean (STD)	51.9 (11.8)	51.0 (11.6)	51.4 (11.7)
Median	51.0	50.0	50.0
Min, Max	26, 80	27, 78	26, 80
Age Category, n (%)			
<65 years	211 (83.4)	208 (83.5)	419 (83.5)
≥65 years	42 (16.6)	41 (16.5)	83 (16.5)
Region, n (%)			
US	16 (6.3)	14 (5.6)	30 (6.0)
Europe	106 (41.9)	104 (41.8)	210 (41.8)
Asia	85 (33.6)	88 (35.3)	173 (34.5)
Other	46 (18.2)	43 (17.3)	89 (17.7)
Race, n (%)			
White	122 (48.2)	122 (49.0)	244 (48.6)
Asian	90 (35.6)	90 (36.1)	180 (35.9)
American Indian or Alaska Native	7 (2.8)	7 (2.8)	14 (2.8)
Black or African American	4 (1.6)	6 (2.4)	10 (2.0)
Other	2 (0.8)	1 (0.4)	3 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)
Not Reportable	19 (7.5)	17 (6.8)	36 (7.2)
Unknown	8 (3.2)	6 (2.4)	14 (2.8)
Ethnicity, n (%)			
Not of Hispanic or Latino/a, or Spanish Origin	176 (69.6)	177 (71.1)	353 (70.3)
Hispanic or Latino/a, or of Spanish Origin	52 (20.6)	50 (20.1)	102 (20.3)
Not Reportable	19 (7.5)	17 (6.8)	36 (7.2)
Unknown	6 (2.4)	5 (2.0)	11 (2.2)

Table 55 Summary of Baseline Disease Characteristics Study SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)	Total (N=502)
ECOG performance status[b], n (%)			
0	137 (54.2)	136 (54.6)	273 (54.4)
1	116 (45.8)	113 (45.4)	229 (45.6)
Prior bevacizumab administration[b], n (%)			
Yes	164 (64.8)	157 (63.1)	321 (63.9)
No	89 (35.2)	92 (36.9)	181 (36.1)
Prior anti-PD-[L]1 administration[b], n (%)			
Yes	71 (28.1)	67 (26.9)	138 (27.5)
No	182 (71.9)	182 (73.1)	364 (72.5)
Histology, n (%)			
Squamous cell carcinoma	160 (63.2)	157 (63.1)	317 (63.1)
Adenocarcinoma	85 (33.6)	75 (30.1)	160 (31.9)
Adenosquamous carcinoma	8 (3.2)	17 (6.8)	25 (5.0)
Tissue factor expression[c], n (%)			
Yes	194 (76.7)	183 (73.5)	377 (75.1)
No	16 (6.3)	11 (4.4)	27 (5.4)
Missing	43 (17.0)	55 (22.1)	98 (19.5)
FIGO stage at initial diagnosis, n (%)			
Stage I to Stage IIA2	54 (21.3)	46 (18.5)	100 (19.9)
Stage IIB	48 (19.0)	52 (20.9)	100 (19.9)
Stage III	6 (2.4)	3 (1.2)	9 (1.8)
Stage IIIA	4 (1.6)	4 (1.6)	8 (1.6)
Stage IIIB, IIIC, IIIC1, IIIC2	67 (26.5)	79 (31.7)	146 (29.1)
Stage IVA	9 (3.6)	7 (2.8)	16 (3.2)
Stage IVB	61 (24.1)	56 (22.5)	117 (23.3)
Unknown	4 (1.6)	2 (0.8)	6 (1.2)
Disease status at study entry, n (%)			
Recurrent	27 (10.7)	24 (9.6)	51 (10.2)
Metastatic	226 (89.3)	225 (90.4)	451 (89.8)
Site(s) of disease at study entry, n (%)			
Bladder	12 (4.7)	6 (2.4)	18 (3.6)
Bone	40 (15.8)	47 (18.9)	87 (17.3)
Bowel	3 (1.2)	4 (1.6)	7 (1.4)
Cervix	129 (51.0)	134 (53.8)	263 (52.4)
CNS	2 (0.8)	2 (0.8)	4 (0.8)
Liver	61 (24.1)	51 (20.5)	112 (22.3)
Lung	113 (44.7)	113 (45.4)	226 (45.0)
Lymph Node	158 (62.5)	161 (64.7)	319 (63.5)
Rectum	12 (4.7)	9 (3.6)	21 (4.2)
Site(s) of disease at study entry, n (%) (cont'd)			
Uterus	21 (8.3)	28 (11.2)	49 (9.8)
Vagina	18 (7.1)	33 (13.3)	51 (10.2)
Other	120 (47.4)	107 (43.0)	227 (45.2)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Baseline disease characteristics are based on the EDC records.
c. Tissue factor (TF) expression is defined as TF membrane expression >=1%.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Table 56 Summary of Prior Systemic and Radiation Therapies and Surgical Treatment SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy[a] (N=249) n (%)	Total (N=502) n (%)
Subjects who received any prior systemic therapy or radiation for cervical cancer	253 (100)	249 (100)	502 (100)
Subjects who received any prior systemic therapy	253 (100)	249 (100)	502 (100)
Subjects who received any prior radiation therapy for cervical cancer	205 (81.0)	203 (81.5)	408 (81.3)
Subjects who received chemo/radiation (without surgery) with curative intent	118 (46.6)	116 (46.6)	234 (46.6)
Subjects who received external beam radiation therapy	198 (78.3)	190 (76.3)	388 (77.3)
Subjects who received brachytherapy	117 (46.2)	121 (48.6)	238 (47.4)
Subjects with bevacizumab in combination with chemotherapy doublet as 1L therapy[b]	155 (61.3)	147 (59.0)	302 (60.2)
Subjects who received any prior surgical treatment for cervical cancer	116 (45.8)	117 (47.0)	233 (46.4)
Number of prior recurrent/metastatic systemic regimens			
1	159 (62.8)	149 (59.8)	308 (61.4)
2	93 (36.8)	100 (40.2)	193 (38.4)
Unknown	1 (0.4)	0	1 (0.2)
Best response to last systemic regimen			
CR	23 (9.1)	21 (8.4)	44 (8.8)
PR	63 (24.9)	52 (20.9)	115 (22.9)
SD	33 (13.0)	52 (20.9)	85 (16.9)
PD	84 (33.2)	85 (34.1)	169 (33.7)
Unknown	47 (18.6)	36 (14.5)	83 (16.5)
Not Applicable	3 (1.2)	3 (1.2)	6 (1.2)

Page 1 of 15

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Regimen can be a combination of individual drugs, for example, BEVACIZUMAB/CISPLATIN/TOPOTECAN.
Medications are sorted by descending order of frequency in total column.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-pr-sys.sas Output:t14-02-05-pr-sys-itt.rtf (30OCT23:14:51) Data: adsl, adctx

Table 57 Summary of Prior Cisplatin and Carboplatin SGNTV-003 ITT Analysis Set

	Tisotumab vedotin (N=253) n (%)	Chemotherapy[a] (N=249) n (%)	Total (N=502) n (%)
Subjects with either prior cisplatin or prior carboplatin	253 (100)	249 (100)	502 (100)
Subjects received prior cisplatin or carboplatin as systemic therapy in recurrent or metastatic setting	250 (98.8)	246 (98.8)	496 (98.8)
Subjects did not receive prior cisplatin or carboplatin as systemic therapy in recurrent or metastatic setting	3 (1.2)	3 (1.2)	6 (1.2)
Subjects received prior topotecan and paclitaxel as systemic therapy in recurrent or metastatic setting	1 (0.4)	1 (0.4)	2 (0.4)
Subjects received prior cisplatin or prior carboplatin in curative setting	3 (1.2)	3 (1.2)	6 (1.2)
Subjects received prior cisplatin or carboplatin as radio sensitiser	3 (1.2)	2 (0.8)	5 (1.0)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Numbers analysed

Table 58 Summary Analysis Sets

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy[a] (N=249) n (%)	Total (N=502) n (%)
Subjects randomized	253	249	502
ITT Analysis Set[b]	253 (100)	249 (100)	502 (100)
Safety Analysis Set[c]	250 (98.8)	239 (96.0)	489 (97.4)
PRO FAS[d]	231 (91.3)	203 (81.5)	434 (86.5)
Pharmacokinetics Analysis Set[e]	231 (91.3)	0	231 (46.0)

ADC=antibody-drug conjugate; FAS=Full Analysis Set; ITT=intent-to-treat; MMAE=monomethyl auristatin E; PRO=patient-reported outcome; TAb=total antibody.

a. The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

b. ITT set includes all randomized subjects. Subjects are included in the treatment group assigned at randomization regardless of any actual treatment received.

c. Safety set includes all randomized subjects who received at least 1 dose of study treatment (tisotumab vedotin or chemotherapy).

d. The PRO FAS set includes all randomized subjects who received any amount of study treatment and have completed baseline and at least 1 post-baseline PRO assessment.

e. Pharmacokinetics set includes all randomized subjects who received any amount of tisotumab vedotin and who have at least 1 reportable value of ADC, TAb, or MMAE concentration.

Outcomes and estimation

Primary endpoint: OS (DCO 24-Jul-2023)

Table 59 Primary endpoint OS in Study SGNTV-003 (ITT Analysis Set)

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Number of deaths, n (%)	123 (48.6)	140 (56.2)
Stratified hazard ratio[b, c] (95% CI)	0.70 (0.54, 0.89)	
Stratified log-rank p-value[c, d]	0.0038	
Median OS (months) (95% CI)[e]	11.5 (9.8, 14.9)	9.5 (7.9, 10.7)
Q1, Q3	6.7, 21.3	4.6, 16.3
Min, Max[f]	0.4, 25.0	0.0+, 21.9+
Median duration of follow-up (months) (95% CI)	10.8 (10.2, 12.1)	10.8 (10.1, 12.2)
Estimated OS rate[e] at		
6 months (95% CI)[e]	81.4 (75.9, 85.7)	66.9 (60.5, 72.5)
12 months (95% CI)[e]	48.7 (41.0, 55.8)	35.3 (28.0, 42.7)
18 months (95% CI)[e]	33.1 (24.2, 42.2)	23.5 (15.8, 32.2)

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; Max=maximum; Min=minimum; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1.

a. The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.

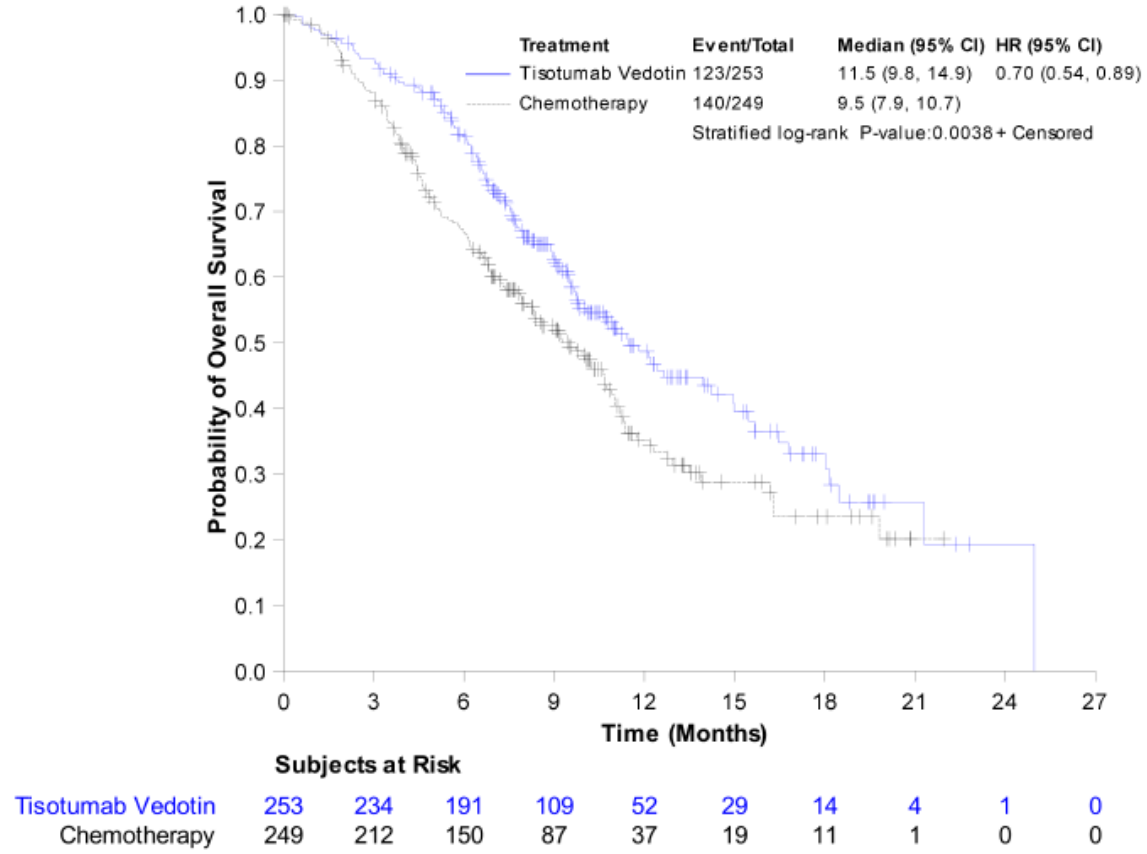
c. Computed using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.

d. Two-sided p-value calculated from stratified log-rank test.

e. Median is estimated using Kaplan-Meier method and 95% CI is calculated using the complimentary log-log transformation method (Collett 1994).

f. '+' means the observed time is from a censored subject.

The threshold for statistical significance is 0.0226 (2-sided).



CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1.

HR is computed from the stratified Cox proportional hazards model using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.

Two-sided p-value based on stratified log-rank test.

Figure 33 Kaplan-Meier Plot of Overall Survival (ITT Analysis Set)

Updated OS (DCO 16-Jan-2024)

An additional 6 months of follow-up with ad-hoc descriptive OS analysis is presented below.

Table 60: Summary of Overall Survival and Duration of Follow-up SGNTV-003 (ITT Analysis Set) (DCO 16-Jan-2024)

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Number of deaths, n (%)	176 (69.6)	174 (69.9)
Stratified hazard ratio[b, c] (95% C.I.)	0.79 (0.63, 0.97)	
Stratified log-rank p-value[c, d]	0.0280	
Median OS (months) (95% C.I.)[e]	11.7 (9.9, 13.1)	9.2 (8.0, 10.3)

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Q1, Q3	6.7, 18.3	4.6, 18.3
Min, Max[f]	0.4, 28.6+	0.0+, 27.9+
Median duration of follow-up (months) (95% C.I.)[e,g]	16.8 (16.0, 18.7)	16.5 (15.5, 17.6)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.
c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
d. Two-sided p-value calculated from stratified log-rank test. Provided as a descriptive nominal p-value.
e. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).
f. '+' means the observed time is from a censored subject.
g. Based on reverse Kaplan-Meier estimates
Snapshot Date: 13FEB2024, Data Cutoff Date: 16JAN2024

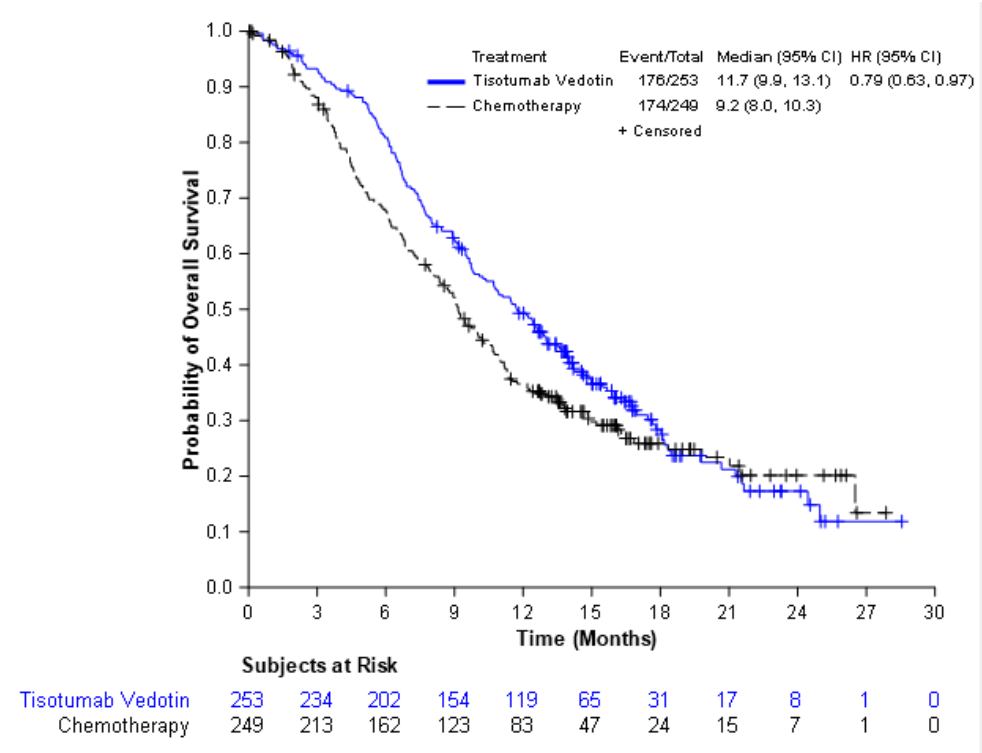


Figure 34: Overall Survival by Treatment Arm SGNTV-003 ITT Analysis Set (DCO 16-Jan-2024)

HR is computed from the stratified Cox proportional hazards model using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
Snapshot Date: 13FEB2024, Data Cutoff Date: 16JAN2024

Secondary endpoints:

- **PFS per Investigator**

Table 61 Summary of PFS per investigator (ITT Analysis Set)

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Subjects with PFS event, n (%)	198 (78.3)	194 (77.9)
Stratified hazard ratio[b,c] (95% CI)	0.67 (0.54, 0.82)	
Stratified log-rank p-value[c,d]	<0.0001	
Median PFS (months) (95% CI)[e]	4.2 (4.0, 4.4)	2.9 (2.6, 3.1)
Q1, Q3	2.7, 7.1	1.4, 5.4
Min, Max[f]	0.0+, 21.0+	0.0+, 20.8+
Estimated PFS rate[e] at		
3 months (95% CI)[e]	62.7 (56.2, 68.4)	45.8 (39.1, 52.2)
6 months (95% CI)[e]	30.4 (24.5, 36.5)	18.9 (13.8, 24.7)
9 months (95% CI)[e]	16.6 (11.7, 22.3)	9.4 (5.5, 14.5)

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; Max=maximum; Min=minimum; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; PFS=progression-free survival.

a. The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.

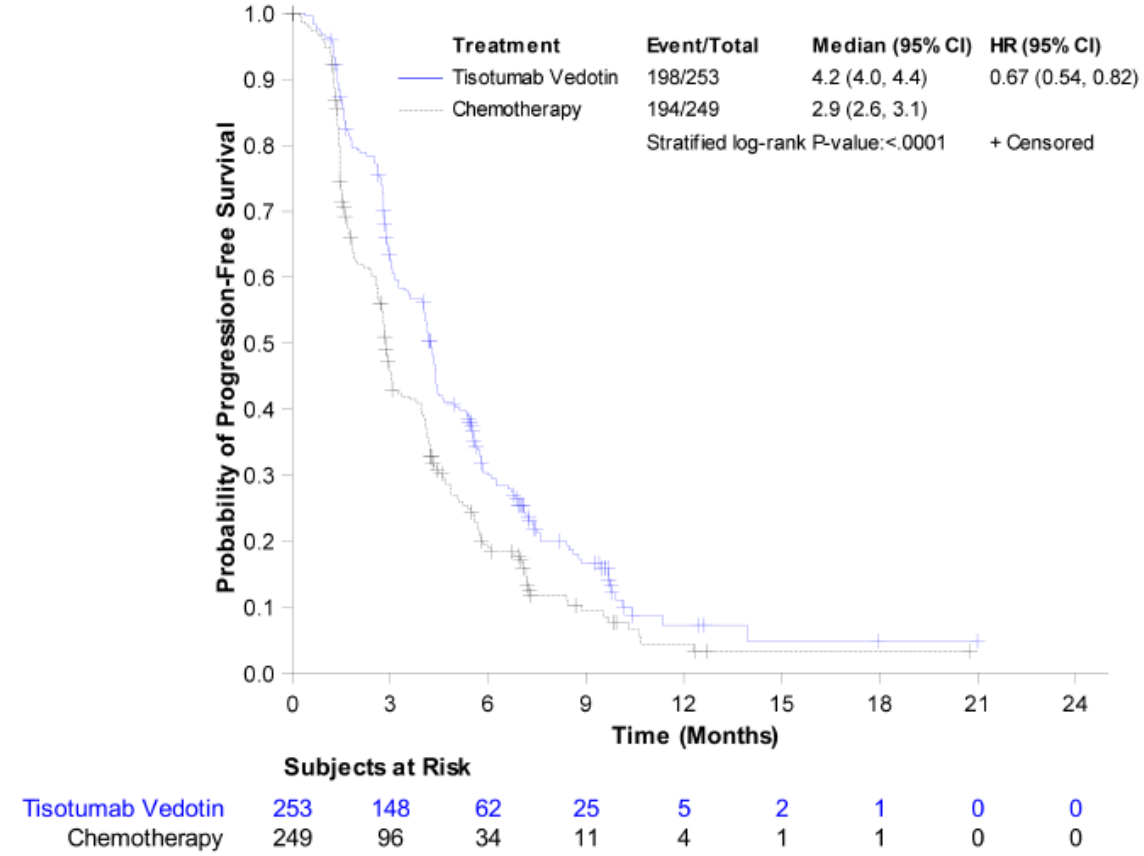
c. Computed using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.

d. Two-sided p-value calculated from stratified log-rank test.

e. Median is estimated using Kaplan-Meier method and 95% CI is calculated using the complimentary log-log transformation method (Collett 1994).

f. '+' means the observed time is from a censored subject.

PFS hypothesis testing will be conducted only when the OS result crosses efficacy boundary. The threshold for statistical significance is 0.0453 (2-sided).



CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; PFS=progression-free survival.

HR is computed from the stratified Cox proportional hazards model using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.

Two-sided p-value based on stratified log-rank test.

Figure 35 Kaplan-Meier Plot of PFS per Investigator (ITT Analysis Set)

- **ORR per Investigator**

Table 62 Objective Response per Investigator (ITT Analys Set)

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Best overall response[b], n (%)		
Complete response (CR)	6 (2.4)	0
Partial response (PR)	39 (15.4)	13 (5.2)
Stable disease (SD)	147 (58.1)	132 (53.0)
Progressive disease (PD)	46 (18.2)	74 (29.7)
Not evaluable (NE)	0	4 (1.6)
Not available[c]	15 (5.9)	26 (10.4)
Objective response rate (CR+PR)[d], n (%)	45 (17.8)	13 (5.2)
95% CI[e] for objective response rate	(13.3, 23.1)	(2.8, 8.8)
Stratified Odds Ratio (95% CI)[f]	4.0 (2.1, 7.6)	
Stratified CMH p-value[f]	<0.0001	
Disease control rate (CR+PR+SD), n (%)	192 (75.9)	145 (58.2)
95% CI[e] for disease control rate	(70.1, 81.0)	(51.8, 64.4)

CI=confidence interval; CMH= Cochran-Mantel-Haenszel; ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; PFS=progression-free survival.

a. The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Best confirmed overall response assessed by investigator per RECIST 1.1.
c. Subjects with no valid post-baseline response assessments before new anti-cancer therapy, EOT, EOS, whichever is the earliest.
d. Objective response is confirmed CR or PR according to RECIST 1.1.
e. Two-sided 95% exact CI, computed using the Clopper-Pearson method (Clopper 1934).
f. Cochran-Mantel-Haenszel method controlling for stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.
ORR hypothesis testing will be conducted only when the OS result crossed efficacy boundary and PFS result also crossed efficacy boundary. The threshold for statistical significance is 0.05 (2-sided).

- **TTR**

Table 63 Time to Confirmed Responses per Investigator ITT Analysis Set-Confirmed Responders

	Tisotumab Vedotin (N=45)	Chemotherapy[a] (N=13)
Time to objective response[b] (months)		
n	45	13
Mean (STD)	2.10 (0.94)	2.07 (0.87)
Median	1.58	1.74
Min, Max	1.2, 4.5	1.2, 3.9

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Objective Response is confirmed CR or PR according to RECIST 1.1.
a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Time from randomization to earliest occurrence of either CR or PR for subjects with confirmed response.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
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- **DOR**

Table 64 Duration of Objective Response per Investigator, ITT Analysis Set-Confirmed Responders

	Tisotumab Vedotin (N=45)	Chemotherapy[a] (N=13)
Median duration of objective response (months) (95% C.I.)[b]	5.3 (4.2, 8.3)	5.7 (2.8, -)
Q1, Q3	3.5, 9.9	3.7, -
Min, Max[c]	2.4, 19.6+	1.6+, 19.4+

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Objective Response is confirmed CR or PR according to RECIST 1.1.
a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).
c. '+' means the observed time is from a censored subject.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
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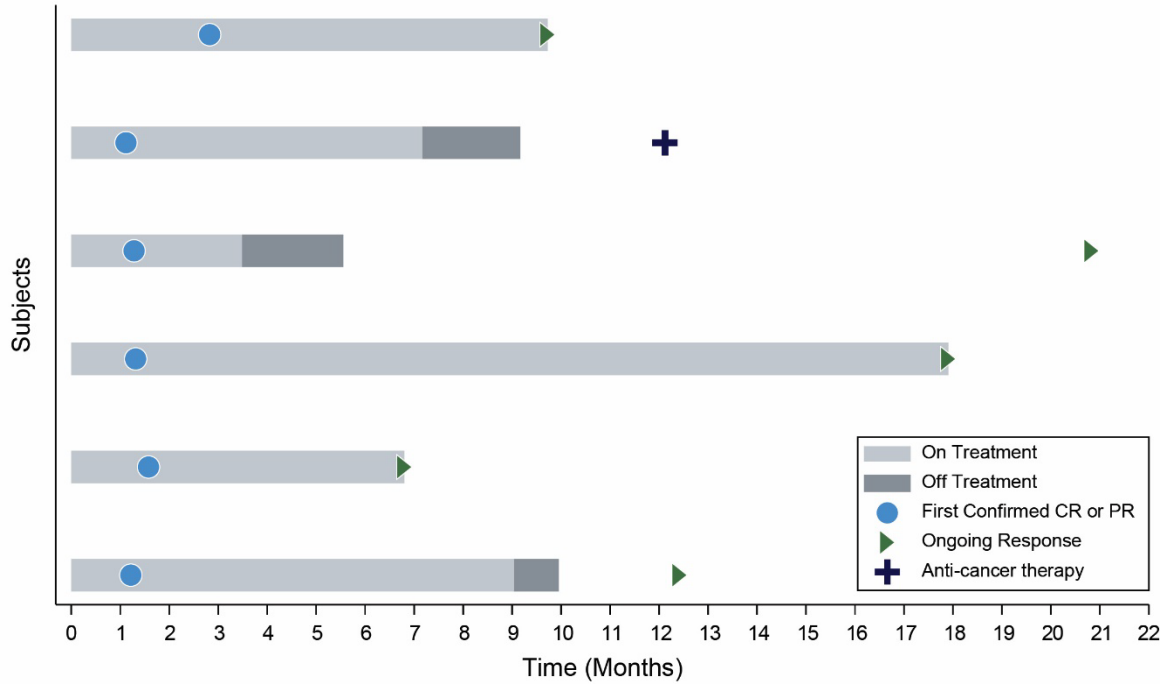

Figure 36. Time to Response and Duration of Response per Investigator SGNTV-003 ITT Analysis Set -- Confirmed Complete Responders

Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

- **PRO (Patient Reported Outcomes)**

Between baseline and Cycle 5, the percentage of subjects who completed the EORTC-QLQ-C30 questionnaire among those included in the PRO FAS population (completion rate) was ≥57.6% in the tisotumab vedotin arm, and ≥38.4% in the chemotherapy arm. The proportion of subjects reporting a ≥10-point improvement from baseline to Cycle 5 in the QLQ-C30 GHS/QOL was 13.9% and 3.4% in the tisotumab vedotin and chemotherapy arms, respectively.

Between baseline and Cycle 5, the compliance rate of the EORTC-QLQ-C24 questionnaire was ≥89.8% in the tisotumab vedotin arm and ≥83.2% in the chemotherapy arm; completion rate was ≥56.3% in the tisotumab vedotin arm and ≥37.9% in the chemotherapy armBetween baseline and Cycle 5, the compliance rate of the EQ-5D questionnaire was ≥88.8% in the tisotumab vedotin arm, and ≥82.4% in the chemotherapy arm; completion rate was ≥57.1% in the tisotumab vedotin arm and ≥40.4% in the chemotherapy arm.

Between baseline and Cycle 5 (median number of cycles received per subject in the tisotumab vedotin arm), patient reported health-related quality of life (QOL), functioning, and symptoms as measured by EORTC QLQ-C30, EORTC QLQ-CX24, and EQ-5D was generally maintained for subjects in the tisotumab vedotin arm.

Relevant questionnaires for assessing PROs were used, however completion of those were voluntary.

Ancillary analyses

- **Subsequent Anti-cancer therapies**

Table 65 Summary of Subsequent Systemic Anti-Cancer Therapies SGNTV-003 ITT Analysis Set

	Tisotumab vedotin (N=253)	Chemotherapy [a] (N=249)	Total (N=502)
Subjects who received any subsequent systemic anti-cancer therapies, n (%)	112 (44.3)	91 (36.5)	203 (40.4)
Number of subsequent systemic regimens, n (%)			
1	79 (31.2)	68 (27.3)	147 (29.3)
2	27 (10.7)	21 (8.4)	48 (9.6)
>=3	6 (2.4)	2 (0.8)	8 (1.6)
Subjects with any subsequent systemic regimens in categories			
Tisotumab vedotin	1/112 (0.9%)	6/91 (6.6%)	7/203 (3.4%)
Cytotoxic chemotherapy	82/112 (73.2%)	57/91 (62.6%)	139/203 (68.5%)
Immunotherapy	35/112 (31.3%)	29/91 (31.9%)	64/203 (31.5%)
Chemo-immunotherapy	7/112 (6.3%)	4/91 (4.4%)	11/203 (5.4%)
Investigational agent	6/112 (5.4%)	7/91 (7.7%)	13/203 (6.4%)
Anti-angiogenic agent	1/112 (0.9%)	1/91 (1.1%)	2/203 (1.0%)
Other/Unknown	2/112 (1.8%)	0/91	2/203 (1.0%)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Weight measured at baseline.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Table 66 Subsequent Anti-cancer therapies analysis SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)	Total (N=502)
Time from last dose of study treatment to first subsequent therapy (weeks)			
n	125	106	231
Mean (STD)	8.5 (5.6)	6.7 (5.7)	7.7 (5.7)
Median	6.7	5.4	6.1
Q1, Q3	5.0, 9.6	3.7, 8.3	4.1, 8.9
Min, Max	1, 35	1, 51	1, 51
Best response to subsequent systemic anti-cancer therapy, n (%)			
CR	0	0	0
PR	6 (2.4)	2 (0.8)	8 (1.6)
SD	5 (2.0)	7 (2.8)	12 (2.4)
PD	34 (13.4)	25 (10.0)	59 (11.8)
Not Evaluable	9 (3.6)	19 (7.6)	28 (5.6)
Missing	58 (22.9)	38 (15.3)	96 (19.1)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-sub-antican.sas Output: t14-02-06-sub-anti-can-itt.rtf (30OCT23:14:52)
Data: adsl, adctx, adpr

Sensitivity analyses

OS

Analysis 1. Unstratified Analysis: OS analysis by unstratified log-rank test to compare the treatment arms. Additionally, an unstratified Cox regression model was to be used to estimate the HR and the corresponding 95% CI for the treatment effect. The same censoring method as for the primary analysis of OS was used.

Table 67 Summary of Sensitivity Analyses of OS SGNTV-003 ITT Analysis Set

	Hazard Ratio[a] (95% CI)
Sensitivity analysis 1	0.71 (0.55, 0.90)
Sensitivity analysis 3[b]	0.65 (0.48, 0.88)

a. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model.
b. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomization, except for sensitivity analysis 1 (do not use stratified analysis) and sensitivity analysis 2 (use eCRF defined strata).
Sensitivity Analysis 1 (Unstratified Analysis): OS analysis use unstratified log-rank test and unstratified cox regression model.
Sensitivity Analysis 3 (Initiation of subsequent cancer-related Therapy): using Inverse probability of censoring weights (IPCW) method, subjects are weighted according to their probability to take subsequent therapy. Subjects who took subsequent therapy will be censored at the time of subsequent cancer-related therapy.
Only applicable sensitivity analysis are presented.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-os-allsens-itt.sas Output: t14-03-03-03-os-allsens-itt.rtf (30OCT23:14:49)
Data: adsl, adtte, adbase

Analysis 3. Subjects who took subsequent therapy were censored at the time of sequent cancer related therapy, but subjects were weighted according to their probability to have taken subsequent therapy.

Table 68 Summary of Overall Survival (OS) Sensitivity 3 (Initiation of Subsequent Cancer Related Therapy) SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Number of deaths, n (%)	62 (24.5)	78 (31.3)
Stratified hazard ratio[b, c] (95% C.I.)	0.65 (0.48, 0.88)	
Median OS (months) (95% C.I.)[d]	21.3 (9.5, -)	10.7 (7.2, 11.7)
Q1, Q3	6.8, -	4.6, -
Min, Max[e]	0.1+, 22.8+	0.0+, 20.9+

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a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model using Inverse probability of censoring weights (IPCW).
c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomization.
d. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).
e. '+' means the observed time is from censored subject.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-os-sens3-itt.sas Output: t14-03-03-06-os-sens3-itt.rtf (30OCT23:14:51)
Data: adsl, adtte, adbase

Table 69: Summary of Overall Survival Sensitivity 4 (RMST)

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
RMST at 21.9 months[b] (95% CI)[c]	12.7 (11.7, 13.7)	10.8 (9.7, 11.8)
RMST different at 21.9 months (tisotumab vedotin - chemotherapy) (95% CI)[d]	1.9 (0.4, 3.4)	

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Restricted mean survival time up to the minimum of month of the latest survival time in either treatment arm.
c. Confidence interval calculated using normal approximation.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

PFS

1. New Subsequent cancer-related therapy before progressive disease (PD)/death: For subjects who received subsequent cancer-related therapy before PD or death, 2 sensitivity analyses were to be performed:

a) Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason.

b) Consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as an event.

2. Missing Tumour Assessments: subjects who missed 2 or more consecutive scheduled assessments before death or PD were considered to have had an event, with the earlier date of death or progression as event date.

Table 70 Summary of Survival Sensitivity of PFS per Investigator SGNTV-003 ITT Analysis Set

	Stratified hazard ratio[a, b] (95% CI)
Sensitivity analysis 1a	0.66 (0.54, 0.81)
Sensitivity analysis 1b	0.66 (0.54, 0.80)
Sensitivity analysis 2	0.68 (0.56, 0.83)

Page 1 of 1

a. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model.
b. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomization, except for sensitivity analysis 4 not shown in the table uses stratification factor from eCRF.
Sensitivity analysis 1a: Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason. A PD or death after a new anti-cancer treatment will still be considered to be a PFS event with the PD date or death date as the PFS date.
Sensitivity Analysis 1b (New Subsequent cancer-related therapy before PD/death): consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as an event at start date of subsequent therapy.
Sensitivity Analysis 2 (Missing Tumor Assessments): consider subjects who missed two or more consecutive scheduled assessments before death or PD as having had an event, with the earlier date of death or progression as event date.
Only applicable sensitivity analysis are presented.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-pfs-allsens-itt.sas Output: t14-03-02-04-pfs-allsens-itt.rtf (30OCT23:14:51) Data: adsl, adtte

Table 71:Summary of Reasons for Study Treatment Discontinuation for Subjects Censored Due to Starting New Anti-Cancer Therapy SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=10) n (%)	Chemotherapy (N=18) n (%)
Subjects who received study treatment	8 (80.0)	16 (88.9)
Subjects with presence of radiographical progression	0	0
Subjects who discontinued study treatment	8 (80.0)	16 (88.9)
Reason for discontinuation from study treatment, treated subjects		
Progressive disease	2 (20.0)	8 (44.4)
Subject decision, non-AE	1 (10.0)	6 (33.3)
Adverse event	4 (40.0)	1 (5.6)
Investigator decision	1 (10.0)	1 (5.6)
Other, non-AE	0	0
Study termination by sponsor	0	0

Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Table 72 Reason for PFS Censoring per Investigator SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253) n (%)	Chemotherapy[a] (N=249) n (%)
Censored subjects	55 (21.7)	55 (22.1)
Reasons for censoring[b]		
New anti-cancer treatment (systemic, radiation, or surgery) started before PD or death observed	10 (18.2)	18 (32.7)
Death or progression right after two or more consecutively missed scheduled tumor assessments	6 (10.9)	5 (9.1)
No adequate post-baseline tumor assessments[c]	2 (3.6)	9 (16.4)
No documented disease progression, still on study	34 (61.8)	20 (36.4)
Off study without events	3 (5.5)	3 (5.5)
Withdrawal of consent	3 (5.5)	2 (3.6)
Lost to follow-up	0	1 (1.8)
Off study without events (cont'd)	3 (5.5)	3 (5.5)
Other	0	0

Page 2 of 2

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Denominator is the number of censored subjects.
c. Censoring date will be date of randomization when subject had no post-baseline tumor assessment and had either no death or death after a prolonged duration (e.g., after the planned 2nd response assessment date).
The ordering of censoring is: 1. New anti-cancer treatment (systemic, radiation, or surgery) started before PD or death observed; 2. Death or PD right after two or more consecutively missed scheduled tumor assessments; 3. No adequate post-baseline tumor assessments; 4. No documented disease, still on study; 5. Off study without events.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-pfs-cnsr-itt.sas Output: t14-03-02-03-pfs-cnsr-itt.rtf (30OCT23:14:51)
Data: adsl, adtte

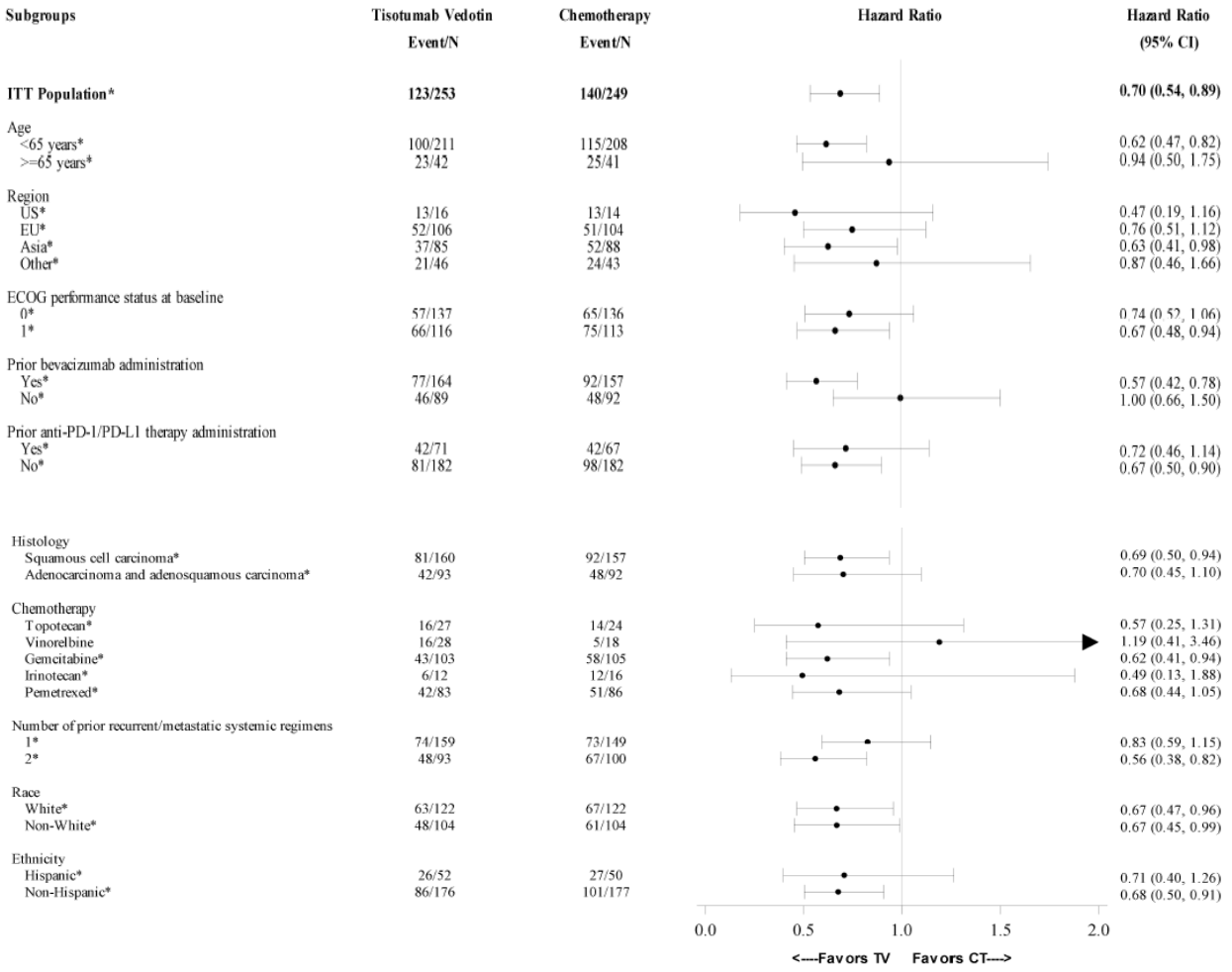
A new sensitivity analysis was conducted using the EMA-preferred approach of PFS censoring rule as follows (EMA 2011): Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason. Not to consider missing two or more missed scheduled tumour scans as a censoring reason (i.e. subjects who died or experienced progressive disease [PD] on or after the start of any subsequent anti-cancer-related therapies, or on or after two or more missed consecutive scheduled tumour scans, are considered to have had a PFS event, with the earlier date of death or progression as event date. Otherwise, subjects are censored at their last tumour scan prior to the data cutoff date.)

Table 73. Summary of Progression-Free Survival per Investigator, Sensitivity 3 SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)
Subjects with progression or death, n (%)	212 (83.8)	208 (83.5)
Stratified hazard ratio[b, c] (95% C.I.)	0.69 (0.57, 0.84)	
Median PFS (months) (95% C.I.)[d]	4.3 (4.0, 4.5)	2.9 (2.7, 3.1)
Q1, Q3	2.7, 7.1	1.5, 5.5
Min, Max[e]	0.0+, 21.0+	0.0+, 20.8+

Subgroup analyses (DCO 24-Jul-2023)

Primary endpoint: OS



CI=confidence interval; CT=chemotherapy; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; TV=tisotumab vedotin.

HR is computed from the Cox proportional hazards model using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.

Chemotherapy subgroups are based on the investigator's pre-specified chemotherapy choice before randomization for each subject if randomized to the chemotherapy arm.

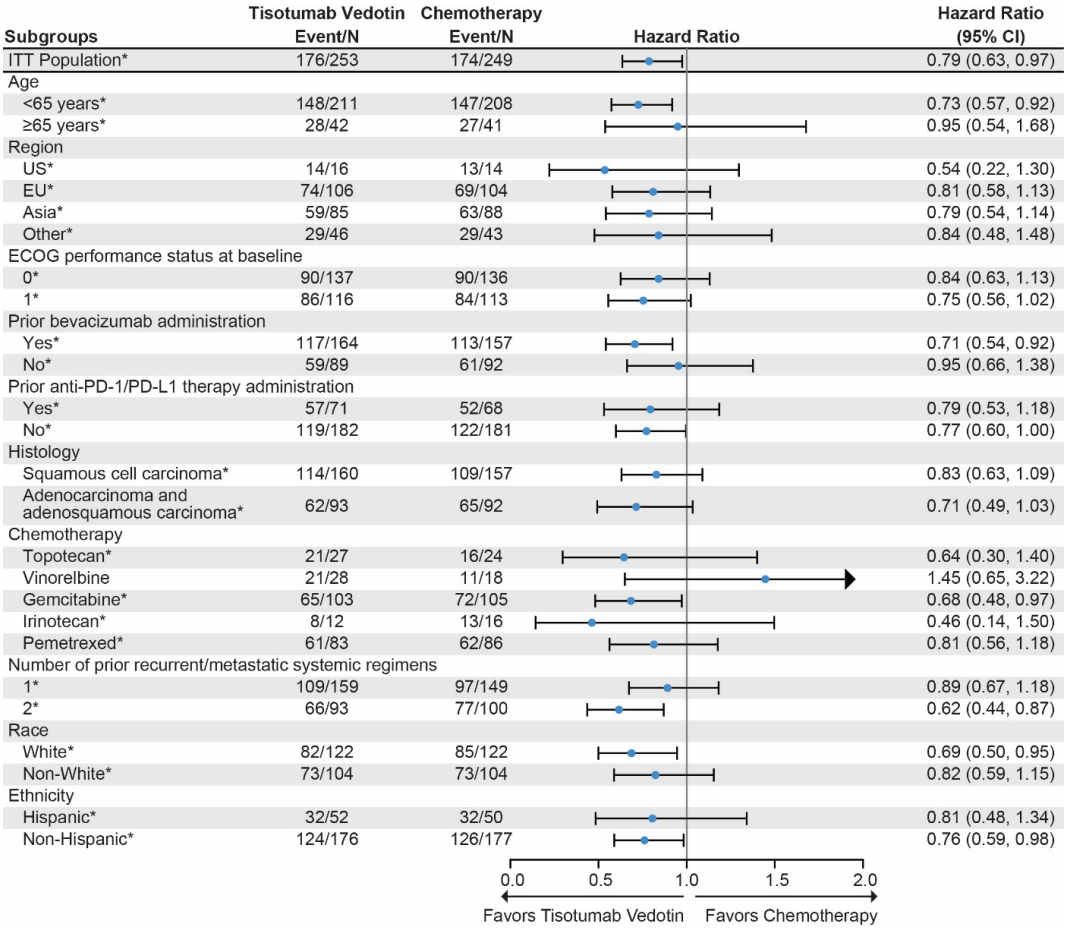
Subgroup except Chemotherapy is defined based on eCRF records. Chemotherapy subgroup is based on RTSM records. If the subgroup is defined by a randomization stratification factor, Cox model is stratified for the randomization stratification factors other than the one that defines the subgroup.

* Indicates subgroup with HR<1.

Figure 37 Forest Plot of OS (ITT Analysis Set)

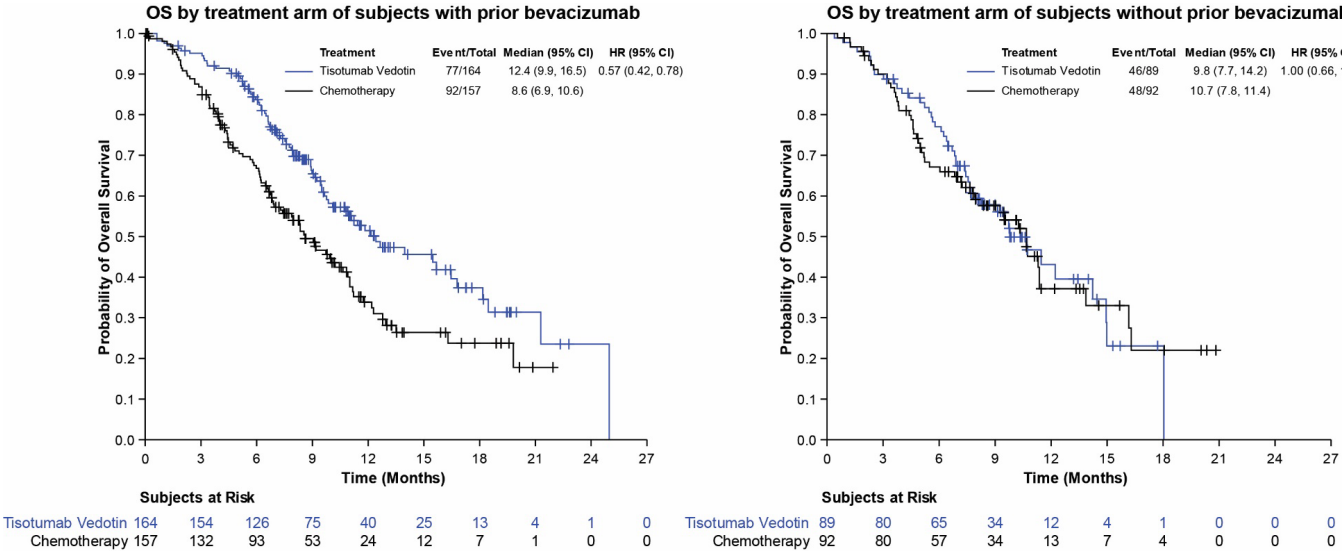
Updated forest plot with DCO 16-Jan-2024

Figure 38: Hazard Ratio and 95% CI for Overall Survival by Subgroups SGNTV-003 ITT Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
Chemotherapy subgroups are based on the investigator's pre-specified chemotherapy choice before randomisation for each subject if randomised to the chemotherapy arm.
Subgroup except Chemotherapy is defined based on eCRF records. Chemotherapy subgroup is based on RTSM records. If the subgroup is defined by a randomisation stratification factor, Cox model is stratified for the randomisation stratification factors other than the one that defines the subgroup.
* Indicates subgroup with HR<1.
TV= Tisotumab Vedotin; CT= Chemotherapy.
Snapshot Date: 13FEB2024, Data Cutoff Date: 16JAN2024

OS for subgroup with prior bevacizumab exposure

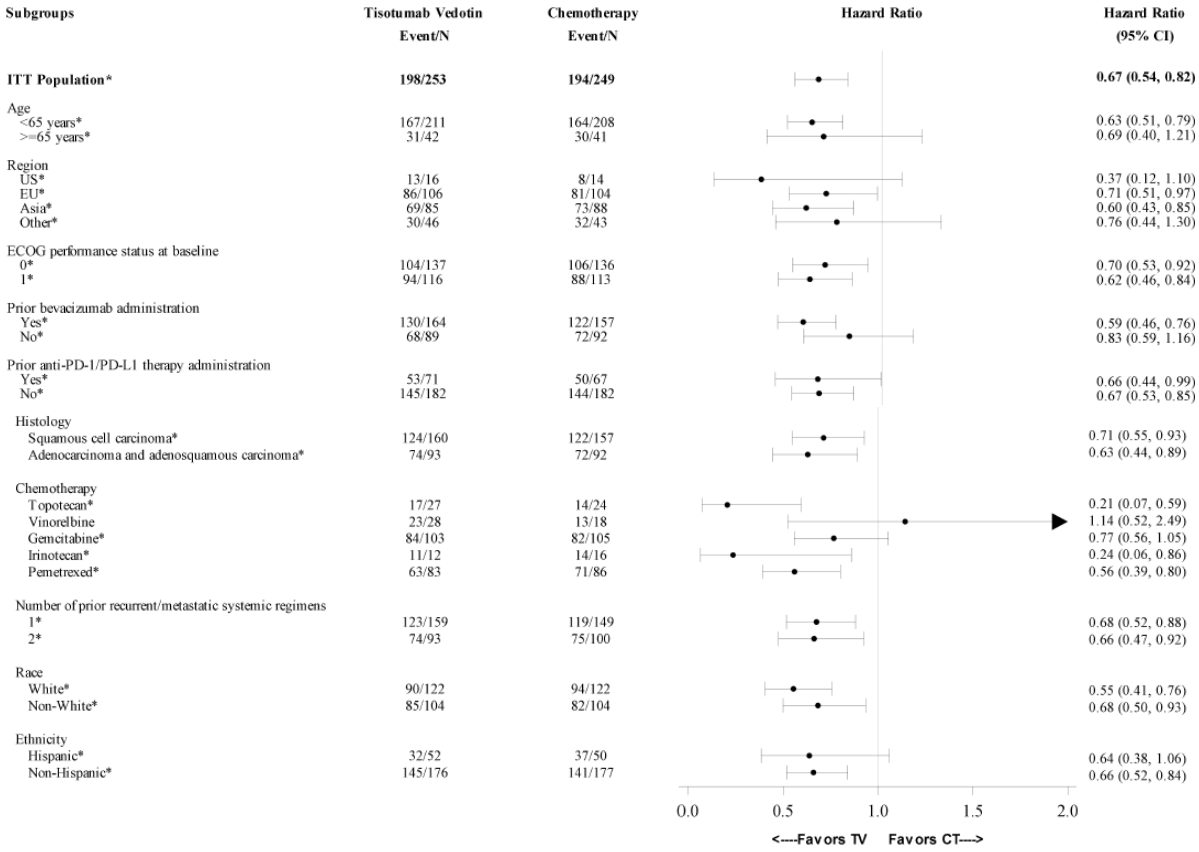


1. HR is computed from the stratified Cox proportional hazards model using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.

Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Figure 39: Overall Survival by Treatment Arm – SGNTV-003 ITT Analysis Set – Prior bevacizumab

Secondary endpoints:



CI=confidence interval; CT=chemotherapy; ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; TV=tisotumab vedotin.

HR is computed from the Cox proportional hazards model using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti-PD-L1 administration: yes vs no) at randomization.

Chemotherapy subgroups are based on the investigator's pre-specified chemotherapy choice before randomization for each subject if randomized to the chemotherapy arm.

Subgroup except Chemotherapy is defined based on eCRF records. Chemotherapy subgroup is based on RTSM records. If the subgroup is defined by a randomization stratification factor, Cox model is stratified for the randomization stratification factors other than the one that defines the subgroup.

* Indicates subgroup with HR<1.

Figure 40 Forest Plot of PFS per Investigator (ITT Analysis Set)

ORR

Exploratory analyses:

Tissue Factor (TF) expression

Table 74 Tissue factor Expression Prevalence SGNTV-003 ITT Analysis Set

TF Expression	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)	Total (N=502)
Number of subjects with evaluable biopsy[b]	210	194	404
TF membrane expression ≥1%, n (%)[c]	194 (92.4)	183 (94.3)	377 (93.3)
TF cytoplasmic expression ≥1%, n (%)[c]	186 (88.6)	180 (92.8)	366 (90.6)

TF=tissue factor
a. The 5 chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Number of subjects with evaluable data. Data was not available for some subjects because of inadequate tissue quality or quantity, or unavailable tissue.
c. Number of subjects with evaluable biopsy is used as the denominator in computing percentage.
Snapshot Date: 21AUG2023, DCO Date: 24JUL2023

Table 75 Tissue factor Expression in Tumours SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)	Total (N=502)
Tumor Membrane H-score at baseline			
n[b]	210	194	404
Mean (STD)	76.8 (74.7)	92.8 (86.6)	84.5 (80.9)
Median	45.0	65.0	55.0
Q1, Q3	13.0, 120.0	17.0, 160.0	14.0, 140.0
Min, Max	0, 291	0, 300	0, 300
Tumor Membrane % Total at baseline			
n[b]	210	194	404
Mean (STD)	38.3 (34.7)	45.1 (37.5)	41.6 (36.2)
Median	25.0	37.5	30.0
Q1, Q3	8.0, 70.0	9.0, 85.0	8.0, 80.0
Min, Max	0, 100	0, 100	0, 100

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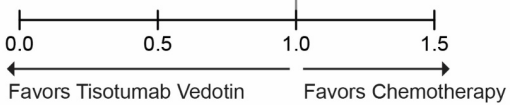
a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan and pemetrexed.
b. Number of subjects with evaluable data. Data was not available for some subjects because of inadequate tissue quality or quantity, or unavailable tissue.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-tf-exp.sas Output: t14-09-05-tf-exp.rtf (30OCT23:14:52) Data: adsl, adtf

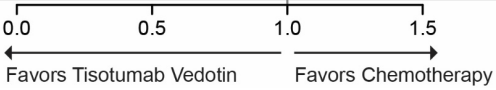
Subgroups	Tisotumab Vedotin Event/N	Chemotherapy Event/N	Hazard Ratio	Hazard Ratio (95% CI)
ITT Population*	**123/253**	**140/249**		**0.70 (0.54, 0.89)**
Tissue factor membrane expression				
<25% Quantile (14)*	30/54	31/46		0.72 (0.42, 1.22)
≥25% Quantile (14)*	72/156	85/148		0.65 (0.47, 0.89)
<Median (55)*	52/110	51/88		0.73 (0.49, 1.10)
≥Median (55)*	50/100	65/106		0.56 (0.38, 0.82)
<75% Quantile (140)*	81/166	78/133		0.70 (0.51, 0.97)
≥75% Quantile (140)*	21/44	38/61		0.49 (0.27, 0.89)
Tissue factor cytoplasmic expression				
<25% Quantile (17.5)*	32/56	30/45		0.77 (0.45, 1.33)
≥25% Quantile (17.5)*	70/154	86/149		0.61 (0.44, 0.85)
<Median (84.5)*	58/111	54/91		0.83 (0.56, 1.24)
≥Median (84.5)*	44/99	62/103		0.53 (0.35, 0.79)
<75% Quanti le (119)*	79/161	85/141		0.74 (0.54, 1.02)
≥75% Quantile (119)*	23/49	31/53		0.49 (0.27, 0.89)



HR is computed from the Cox proportional hazards model using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
* Indicates subgroup with HR<1.
TV= tisotumab vedotin; CT= Chemotherapy.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Figure 41: Hazard Ratio and 95% CI for Overall Survival by Subgroup SGNTV-003 ITT Analysis Set

Subgroups	Tisotumab Vedotin Event/N	Chemotherapy Event/N	Hazard Ratio	Hazard Ratio (95% CI)
ITT Population*	**198/253**	**194/249**		**0.67 (0.54, 0.82)**
Tissue factor membrane expression				
<25% Quantile (14)*	43/54	36/46		0.57 (0.35, 0.93)
≥25% Quantile (14)*	122/156	124/148		0.62 (0.48, 0.81)
<Median (55)*	86/110	70/88		0.75 (0.54, 1.05)
≥Median (55)*	79/100	90/106		0.54 (0.39, 0.75)
<75% Quantile (140)*	129/166	107/133		0.74 (0.57, 0.97)
≥75% Quantile (140)*	36/44	53/61		0.38 (0.22, 0.64)
Tissue factor cytoplasmic expression				
<25% Quantile (17.5)*	45/56	36/45		0.80 (0.48, 1.31)
≥25% Quantile (17.5)*	120/154	124/149		0.58 (0.45, 0.76)
<Median (84.5)*	86/111	70/91		0.83 (0.59, 1.16)
≥Median (84.5)*	79/99	90/103		0.48 (0.34, 0.67)
<75% Quantile (119)*	127/161	114/141		0.72 (0.55, 0.93)
≥75% Quantile (119)*	38/49	46/53		0.39 (0.24, 0.65)



HR is computed from the Cox proportional hazards model using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
* Indicates subgroup with HR<1.
TV= tisotumab vedotin; CT= Chemotherapy.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Figure 42: Hazard Ratio and 95% CI for Progression Free Survival per Investigator by Subgroups SGNTV-003 ITT Analysis Set

Post-hoc analysis

Platinum-free interval

Platinum-free interval was defined as the time from last platinum-based chemotherapy date in the recurrent/metastatic setting to documented progression date. The platinum-free interval was set to 0 if the last platinum-based treatment end date was after progression date. For subjects with missing or partial disease progression and treatment end dates, these were imputed as the 15th day of the month if both month and year were present and only day was missing.

Table 76:Summary of Platinum-Free Interval SGNTV-003 ITT Analysis Set – Subjects Received Platinum-based therapy in recurrent/metastatic setting

	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=246) n (%)	Total (N=496) n (%)
Platinum-free interval (months)[b]			
n	129	115	244
Mean (STD)	1.2 (1.7)	0.8 (1.3)	1.0 (1.5)
Median	0.7	0.5	0.5
Q1, Q3	0.3 , 1.1	0.2 , 0.8	0.2 , 0.9
Min, Max	0, 9	0, 9	0, 9

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Platinum-free interval is the interval from last dose of platinum to progression as defined per investigator.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 77 Summary of efficacy for trial SGNTV-003

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		
Study identifier	SGNTV-003 EU Trial No.: 2023-503813-31 EudraCT#2019-001655-39 ENGOT Study#ENGOT-cx12 GOG Study#GOG-3057 NCT04697628	
Design	A phase 3 randomised, open-label multi-centre, global study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years 4 months not applicable not applicable
Hypothesis	Superiority	

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			
Study identifier	SGNTV-003 EU Trial No.: 2023-503813-31 EudraCT#2019-001655-39 ENGOT Study#ENGOT-cx12 GOG Study#GOG-3057 NCT04697628		
Treatments groups	Tisotumab vedotin		Tisotumab vedotin intravenous (IV) infusion 2.0 mg/kg (up to a maximum of 200 mg for patients ≥100 kg) on day 1 of each 21-day treatment cycle for unlimited cycles or until at least 1 discontinuation criterion was met or upon study termination, whichever occurred first. Randomised n=253 subjects Treated n=250 subjects
	Investigator's Choice Chemotherapy		Chemotherapy options in the comparator arm were: • 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 Randomised n=249 subjects Treated n=239 subjects
Endpoints and definitions	Primary endpoint Overall Survival	OS	OS was defined as the time from the date of randomisation to the date of death due to any cause.
	Key Secondary endpoint: Progression-free Survival	PFS per investigator	PFS per investigator was defined as the time from the date of randomisation 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 occurred earlier.
	Key Secondary endpoint: Confirmed objective response rate (complete response [CR] + partial response [PR])	cORR per investigator	Confirmed ORR was defined as the proportion of participants with a confirmed complete response (CR) or partial response (PR) per RECIST v.1.1. Tumour images were reviewed by the local investigator.
	Secondary endpoint: Duration of response	DOR per investigator	DOR was summarised descriptively by treatment group using the Kaplan-Meier approach. Only subjects with confirmed CR or PR were included.
Database lock	24-Jul-2023		
Results and Analysis			
Analysis description	**Primary Analysis OS**		

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			
Study identifier	SGNTV-003 EU Trial No.: 2023-503813-31 EudraCT#2019-001655-39 ENGOT Study#ENGOT-cx12 GOG Study#GOG-3057 NCT04697628		
Analysis population and time point description	Intent to treat (ITT) Analysis Set (all randomised subjects) As of data cutoff date of 24-Jul-2023		
Descriptive statistics and estimate variability	Treatment group	Tisotumab vedotin	Chemotherapy
	Number of subjects (N)	253	249
	Number of deaths, n (%)	123(48.6)	140(56.2)
	OS (months) Median OS[a] (95% CI)[b]	 11.5 (9.8, 14.9)	 9.5 (7.9, 10.7)
Effect estimate per comparison	Stratified Hazard Ratio	0.70	
	(95% CI)[c]	(0.54,0.89)	
	2-sided p-valued [d]	0.0038	
Notes	a. Median is estimated using Kaplan-Meier method. b. 95% CI calculated using the complimentary log-log transformation method. c. Calculated from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group [ECOG] performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein1 [PD-1] or anti-programmed cell death ligand 1 [PD-L1]; administration: yes vs no) at randomisation. d. Two-sided p-value calculated from stratified log-rank test. The threshold for statistical significance for OS is 0.0226 (2-sided).		
Analysis description	**Secondary Analysis PFS**		
Analysis population and time point description	Intent to treat (ITT) Analysis Set (all randomised subjects) As of data cutoff date of 24-Jul-2023		
Descriptive statistics and estimate variability	Treatment group	Tisotumab vedotin	Chemotherapy
	Number of subjects (N)	253	249
	PFS (months) Median PFS[a] (95% CI)[b]	 4.2 (4.0,4.4)	 2.9 (2.6,3.1)
Effect estimate per comparison	Stratified Hazard Ratio	0.67	
	(95% CI)[c]	(0.54,0.82)	
	2-sided p-valued [d]	<0.0001	

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			
Study identifier	SGNTV-003 EU Trial No.: 2023-503813-31 EudraCT#2019-001655-39 ENGOT Study#ENGOT-cx12 GOG Study#GOG-3057 NCT04697628		
Notes	a. Median is estimated using Kaplan-Meier method. b. 95% CI calculated using the complimentary log-log transformation method. c. Calculated from the Cox proportional hazards model using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti PD L1 administration: yes vs no) at randomisation. d. Two-sided p-value calculated from stratified log-rank test. The threshold for statistical significance for PFS is 0.0453 (2-sided).		
Analysis description	**Secondary Analysis cORR**		
Analysis population and time point description	Intent to treat (ITT) Analysis Set (all randomised subjects) As of data cutoff date of 24-Jul-2023		
Descriptive statistics and estimate variability	Treatment group	Tisotumab vedotin	Chemotherapy
	Number of subjects (N)	253	249
	Best overall response[a] n (%) Complete response (CR) Partial response (PR) cORR, n (%) (95% CI[b] for cORR)	 6 (2.4) 39 (15.4) 45 (17.8) (13.3, 23.1)	 0 13 (5.2) 13 (5.2) (2.8, 8.8)
Effect estimate per comparison	Stratified Odds Ratio	4.0	
	(95% CI)[c]	(2.1, 7.6)	
	Stratified CMH p-value [c,d]	<0.0001	
	Disease Control Rate (DCR)[e], n(%) (95% CI[b] for DCR)	192 (75.9) (70.1, 81.0)	145 (58.2) (51.8, 64.4)
Notes	a. Median is estimated using Kaplan-Meier method. b. 95% CI calculated using the complimentary log-log transformation method. c. Calculated from the Cox proportional hazards model using stratification factors (ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-PD-1 or anti PD L1 administration: yes vs no) at randomisation. d. Two-sided p-value calculated from stratified log-rank test. The threshold for statistical significance for PFS is 0.0453 (2-sided).		
Analysis description	**Secondary Analysis DOR**		
Analysis population and time point description	Intent to treat (ITT) Analysis Set (all randomised subjects) As of data cutoff date of 24-Jul-2023		
Descriptive statistics and estimate variability	Treatment group	Tisotumab vedotin	Chemotherapy
	Number of subjects (N)	45	13
	DOR (months) Median DOR (95% CI)[a]	 5.3 (4.2, 8.3)	 5.7 (2.8, -)

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	
Study identifier	SGNTV-003 EU Trial No.: 2023-503813-31 EudraCT#2019-001655-39 ENGOT Study#ENGOT-cx12 GOG Study#GOG-3057 NCT04697628
Notes	a. As estimated using Kaplan-Meier methods and 95% CI is calculated using the complimentary log-log transformation method.

2.4.5.3. Clinical studies in special populations

Table 78: Summary of Demographics and Baseline Subject Characteristics SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=253)	Chemotherapy [a] (N=249)	Total (N=502)
Age Category, n (%)			
<65 years	211 (83.4)	208 (83.5)	419 (83.5)
>=65 years, < 75 years	34 (13.4)	36 (14.5)	70 (13.9)
>=75 years, < 85 years	8 (3.2)	5 (2.0)	13 (2.6)
>=85 years	0	0	0

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

Table 79: Summary of Confirmed OS PFS and ORR per Investigator SGNTV-003 ITT Analysis Set

	Tisotumab Vedotin (N=211)	**Chemotherapy[a] (N=208)**	**Tisotumab Vedotin (N=211)**	**Chemotherapy[a] (N=208)**	**Tisotumab Vedotin (N=211)**	**Chemotherapy[a] (N=208)**
	Age<65 years	**Age<65 years**	**>=65 years, < 75 years**	**>=65 years, < 75 years**	**>=75 years, < 85 years**	**>=75 years, < 85 years**
Overall Survival (OS)						
Number of deaths, n (%)	100 (47.4)	115 (55.3)	20 (58.8)	22 (61.1)	3 (37.5)	3 (60.0)
Stratified hazard ratio[b, c] (95% C.I.)	0.62 (0.47, 0.82)		1.06 (0.50, 2.21)		- (-, -)	
Median OS (months) (95% C.I.)[d]	11.8 (9.9, 15.0)	9.2 (7.8, 10.7)	8.9 (6.7, -)	11.0 (5.1, 13.9)	- (3.6, -)	10.0 (4.4, -)
Q1, Q3	6.9, 18.5	4.6, 16.3	5.8, -	3.8, 16.3	7.4, -	6.0, -
Min, Max[e]	0.4, 25.0	0.0+, 20.8+	2.3, 18.8+	0.1+, 21.9+	3.6, 19.4+	4.4, 17.0+
Progression-Free Survival (PFS)						
Subjects with a PFS event, n (%)	167 (79.1)	164 (78.8)	27 (79.4)	25 (69.4)	4 (50.0)	5 (100.0)

	Tisotumab Vedotin (N=211)	Chemotherapy[a] (N=208)	Tisotumab Vedotin (N=211)	Chemotherapy[a] (N=208)	Tisotumab Vedotin (N=211)	Chemotherapy[a] (N=208)
Stratified hazard ratio[b, c] (95% C.I.)	0.63 (0.51, 0.79)		0.94 (0.49, 1.78)		- (-, -)	
Median PFS (months) (95% C.I.)[d]	4.2 (4.0, 4.4)	2.8 (2.6, 3.0)	3.6 (2.5, 5.3)	4.0 (1.7, 5.7)	9.9 (3.6, -)	3.0 (1.2, -)
Q1, Q3	2.7, 6.9	1.4, 4.9	2.3, 6.8	1.6, 8.4	5.1, 9.9	1.3, 5.4
Min, Max[e]	0.0+, 21.0+	0.0+, 12.3+	0.0+, 17.9+	0.0+, 20.8+	0.0+, 9.9	1.2, 6.0
Objective Response Best overall response[b], n (%)						
Complete response (CR)	4 (1.9)	0	1 (2.9)	0	1 (12.5)	0
Partial response (PR)	31 (14.7)	8 (3.8)	5 (14.7)	5 (13.9)	3 (37.5)	0
Stable disease (SD)	126 (59.7)	112 (53.8)	18 (52.9)	17 (47.2)	3 (37.5)	3 (60.0)
Progressive disease (PD)	38 (18.0)	63 (30.3)	8 (23.5)	9 (25.0)	0	2 (40.0)
Not evaluable (NE)	0	4 (1.9)	0	0	0	0
Not available[c]	12 (5.7)	21 (10.1)	2 (5.9)	5 (13.9)	1 (12.5)	0
Objective response rate (CR+PR)[d], n (%)	35 (16.6)	8 (3.8)	6 (17.6)	5 (13.9)	4 (50.0)	0
95% CI[e] for objective response rate	(11.8, 22.3)	(1.7, 7.4)	(6.8, 34.5)	(4.7, 29.5)	(15.7, 84.3)	(47.8, 100.0)
Disease control rate (CR+PR+SD), n (%)	161 (76.3)	120 (57.7)	24 (70.6)	22 (61.1)	7 (87.5)	3 (60.0)
95% CI[e] for disease control rate	(70.0, 81.9)	(50.7, 64.5)	(52.5, 84.9)	(43.5, 76.9)	(47.3, 99.7)	(14.7, 94.7)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.
c. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomisation.
d. Median is estimated using Kaplan-Meier method and 95% C.I. is calculated using the complimentary log-log transformation method (Collett, 1994).
e. '+' means the observed time is from a censored subject.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

2.4.5.4. In vitro biomarker test for patient selection for efficacy

Scientific rationale,_TF prevalence in cervical carcinoma, and relation to disease mechanism:

Tissue Factor (TF), also called thromboplastin, CD142 or coagulation factor III, is a 43-47 kDa single chain, integral transmembrane glycoprotein. TF is the main physiological initiator of the TF pathway (extrinsic pathway) of blood coagulation. Binding of the circulating serine protease FVII or FVIIa to membrane-bound TF leads to activation of factor X (FX), generating activated factor X (FXa), eventually leading to thrombin generation and clotting (Mackman 2004). In addition to the activation of the coagulation pathway, activation of TF by FVIIa binding can initiate an intracellular signaling cascade via activation of protease-activated receptor 2 (PAR2) (Coughlin 2000). Signaling pathways activated by TF:FVIIa and thrombin are involved in upregulation of vascular endothelial growth factor

(VEGF) and interleukin-8 (IL-8) production, angiogenesis, cell adhesion, motility and survival (Abe 1999; Bluff 2008). In addition to its role as a pro-coagulant activator, TF plays a role in both vasculogenesis in the developing animal and angiogenesis in normal and malignant adult tissues (Carmeliet 1996; Griffin 2001).

The expression of tissue factor is upregulated in cancer through oncogenic events, such as constitutive activation of the MAPK and PI3K signaling pathways, hypoxia-induced signaling, and loss of tumour suppressor genes (van den Berg 2012). TF is aberrantly expressed in a broad range of tumour types, often correlating with increased metastatic properties and poor disease prognosis, including cervical cancer. (Kakkar 1995; Rickles 1995; Sawada 1999; Wojtukiewicz 1999; Kaushal 2008; Cocco 2011; de Bono 2023). Zhao et al., reported that high level of TF expression had negative prognosis in cervical cancer. (Zhao 2018; de Bono 2023). In cervical carcinoma, TF expression exhibited a prevalence of approximately 94-100% (de Bono 2023).

Table 80:Expression of Tissue Factor in Baseline Clinical Tumour Samples by IHC

	TV Clinical Studies		
	GCT1015-04 r/mCC	SGNTV-003 (r/mCC TV monotherapy arm)	SGNTV-003 (r/mCC Chemotherapy arm)
Number of subjects with evaluable biopsy	80	210	194
TF membrane expression ≥1	77 (96%)	194 (92.4%)	183 (94.3%)
Membrane H Score			
Mean (STD)	109.7 (78.3)	76.8 (74.7)	92.8 (86.6)
Median	120	45	65.0
Min, Max	0; 265	0, 291	0,300
Cytoplasm H Score			
Mean (STD)	94.5 (68.7)	73.8 (59.0)	81.6 (65.4)
Median	100	65	93.5
Min, Max	0; 260	0, 215	0, 260
Membrane TF Tumour Positive (%) a			
Mean (STD)	55.3 (36.0)	38.3 (34.7)	45.1 (37.5)
Median	60	25	37.5
Min, Max	0, 100	0, 100	0, 100
Cytoplasm TF Tumour Positive (%) b			
Mean (STD)	55.8 (36.5)	53.6 (39.3)	57.7 (39.7)
Median	67.5	60	79
Min, Max	0, 100	0, 100	0, 100

r/mcc=recurrent or metastatic cervical cancer; STD=standard deviation; TF=tissue factor; TV=tisotumab vedotin
[a] Positivity defined as the percentage of cells with membrane staining (partial or complete) at any intensity (1+, 2+, 3+).
[b] Positivity defined as the percentage of cells with cytoplasmic staining at any intensity (1+, 2+, 3+)

TF expression assay analytical method

The TF assay was developed as a semiquantitative IHC assay of TF in formalin-fixed paraffin-embedded (FFPE) human tissue using the Ventana BenchMark Ultra automated slide stainer and OptiView DAB IHC Detection System. Analytical assay validation was performed by Roche CDx Pharma Services Laboratory on formalin-fixed specimens only. Assay performance in tissues that have been treated in other fixatives has not been determined.

TF expression was reported using the H-score that considers both staining intensity and the percentage of cells stained at a specific range of intensities. The H-score was calculated by summing the products of the percentages of cells stained at a given intensity (0 - 100) and the staining intensity (0 - 3; 0 = no stain, 1 = low intensity, 2 = medium intensity, 3 = high intensity): H-score = [1 x (% cells with intensity of 1)] + [2 x (% cells with intensity of 2)] + [3 x (% cells with intensity of 3)] The IHC H-score range was 0 to 300.

TF expression assay analytical validation

The TF IHC assay was used retrospectively. Validation was performed at Roche CDx CAP/CLIA Laboratory per College of American Pathologists (CAP) Principles of Analytical Validation of Immunohistochemistry Assays and Clinical Laboratory Improvement Amendments (CLIA) standards for assay validations for research use only.

TF expression assay clinical validity

Clinical validation has not been performed for the TF IHC assay.

TF expression cut-point selection and validation

The TF IHC assay was validated for exploratory purposes and has been used to assess TF expression retrospectively in patient tumours for tisotumab vedotin clinical studies in cervical carcinoma. Clinical validation has not been performed. Responses have been observed across the range of TF levels, suggesting no evidence of an expression-response relationship, nor an Hscore cut-point to differentiate between responders and non-responders. In summary, patients with cervical cancer have derived clinical benefit from tisotumab vedotin irrespective of TF expression level and no clinical cut-point has been selected and validated for this assay.

2.4.5.5. Supportive study(ies)

Study GCT1015-04

Study design: phase 2, open-label, multicentre (36 sites in Europe and the US: Belgium, Czech Republic, Germany, Denmark, Spain, Italy, Sweden, US), single-arm study

Initiation date: 06 June 2018

Completion date: 24 May 2022

Study population: 101 subjects with r/mCC who had received 1 or 2 prior systemic therapy regimens.

Treatment: tisotumab vedotin 2.0 mg/kg (up to a maximum of 200 mg for subjects ≥100 kg) Q3W until disease progression or unacceptable toxicity.
Primary endpoint: confirmed ORR as assessed by an IRC using RECIST v1.1.

Secondary endpoints:

- DOR based upon RECIST v1.1 assessed by the IRC
- Confirmed ORR based upon RECIST v1.1 assessed by the investigator
- DOR based upon RECIST v1.1 assessed by the investigator

Tumour response assessments: every 6 weeks for the first 30 weeks and every 12 weeks thereafter.
Statistical methods: The primary analysis of the trial was based on a data cutoff which ensured all responders were followed for ≥6 months.

H0: $\theta \leq 11\%$ vs HA: $\theta > 11\%$

where θ is the ORR. The test was performed as an exact test at a 1-sided 2.5% significance level. The analysis was performed on the FAS with an intention-to-treat approach so that any subjects with missing information regarding response to treatment were counted as non-responders. In addition, an exact 95% 2-sided confidence interval (CI) for the ORR was provided using the Clopper-Pearson method.

Main inclusion and exclusion criteria:
Eligible subjects were:

- 18 years or older;
- had recurrent or extra-pelvic recurrent or metastatic cervical cancer of squamous cell, adenocarcinoma, or adeno-squamous histology;
- had experienced disease progression during or after treatment with a doublet chemotherapeutic regimen of paclitaxel + cisplatin/carboplatin or paclitaxel+ topotecan, in combination with bevacizumab (if eligible to receive bevacizumab);
- had received no more than 2 prior systemic lines for recurrent or metastatic cancer (chemotherapy administered in the adjuvant or neoadjuvant setting or in combination with radiotherapy was not counted as a prior systemic line);
- had measurable disease according to RECIST v1.1 as assessed by the IRC;
- had acceptable organ function and haematological status;
- had an Eastern Cooperative Oncology Group performance status of 0 or 1.

Tumour biomarker expression was not a criterion for enrolment.

Subjects were excluded if:

- they had received more than 2 prior systemic treatment lines for recurrent or metastatic cervical cancer;
- had past or current coagulation defects;
- had ongoing major bleeding;
- had other malignancy than the inclusion diagnosis (except non-invasive basal cell or squamous cell skin carcinoma, non-invasive, superficial bladder cancer, or any curable cancer with a complete response [CR] of ≥5 years duration);
- had active ocular surface disease;
- had peripheral neuropathy ≥ grade 2.

Results:

Table 81; Summary of treatment disposition ITT Analysis Set (SGNTV-003) and full analysis set (GCT1015-04)

	SGNTV-003[a]		GCT1015-04[a]
	Tisotumab Vedotin (N=253) n (%)	Chemotherapy[b] (N=249) n (%)	Tisotumab Vedotin (N=101) n (%)
Subjects randomized/enrolled	253 (100)	249 (100)	101 (100)
Subjects received at least one dose of study treatment	250 (98.8)	239 (96.0)	101 (100)
Subjects on study treatment	21 (8.3)	16 (6.4)	4 (4.0)
Subjects off study treatment	229 (90.5)	223 (89.6)	97 (96.0)
Reason for treatment discontinuation			
Progressive disease[c]	177 (70.0)	193 (77.5)	74 (73.3)
Adverse event	40 (15.8)	9 (3.6)	13 (12.9)
Investigator decision	2 (0.8)	3 (1.2)	1 (1.0)
Subject decision, non-AE	8 (3.2)	17 (6.8)	5 (5.0)
Study termination by sponsor	0	0	0
Other, non-AE	2 (0.8)	1 (0.4)	0
Death[d]	0	0	4 (4.0)

a. SGNTV-003 is a randomized study and GCT1015-04 is a single-arm study.
b. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
c. Including both radiographic disease progression and clinical progression.
d. Not a reason for treatment discontinuation for SGNTV-003.
Data Cutoff Date: SGNTV-003: 24Jul2023, GCT1015-04: 06Feb2020

Table 82 Summary of demographics and baseline characteristics (SGNTV-003 ITT Analysis Set and GCT1015-04 (full Analysis set)

	SGNTV-003		GCT1015-04
	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)	Tisotumab Vedotin (N=101)
Age (years)			
n	253	249	101
Mean (STD)	51.9 (11.8)	51.0 (11.6)	50.7 (10.7)
Median	51.0	50.0	50.0
Q1, Q3	43.0, 61.0	43.0, 59.0	43.0, 58.0
Min, Max	26, 80	27, 78	31, 78
Age Category, n (%)			
<65 years	211 (83.4)	208 (83.5)	88 (87.1)
≥65 years	42 (16.6)	41 (16.5)	13 (12.9)
Region, n (%)			
US	16 (6.3)	14 (5.6)	15 (14.9)
EU	106 (41.9)	104 (41.8)	86 (85.1)
Asia	85 (33.6)	88 (35.3)	0
Other[b]	46 (18.2)	43 (17.3)	0
Ethnicity, n (%)			
Hispanic or Latino	52 (20.6)	50 (20.1)	6 (5.9)
Not Hispanic or Latino	176 (69.6)	177 (71.1)	95 (94.1)
Not Reportable/Unknown/Missing	25 (9.9)	22 (8.8)	0
Race, n (%)			
American Indian or Alaska Native	7 (2.8)	7 (2.8)	0
Asian	90 (35.6)	90 (36.1)	2 (2.0)
Black or African American	4 (1.6)	6 (2.4)	1 (1.0)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	0
White	122 (48.2)	122 (49.0)	96 (95.0)
Other	2 (0.8)	1 (0.4)	2 (2.0)
Not Reportable/Unknown/Missing	27 (10.7)	23 (9.2)	0
ECOG performance status, n (%)			
0	137 (54.2)	136 (54.6)	59 (58.4)

	SGNTV-003		GCT1015-04
	Tisotumab Vedotin (N=253)	Chemotherapy[a] (N=249)	Tisotumab Vedotin (N=101)
1	116 (45.8)	113 (45.4)	42 (41.6)
Histology, n (%)			
Adenocarcinoma	85 (33.6)	75 (30.1)	27 (26.7)
Adenosquamous Carcinoma	8 (3.2)	17 (6.8)	5 (5.0)
Squamous Cell Carcinoma	160 (63.2)	157 (63.1)	69 (68.3)
Prior bevacizumab administration, n (%)			
Yes	164 (64.8)	157 (63.1)	70 (69.3)
No	89 (35.2)	92 (36.9)	31 (30.7)
Prior anti-PD-[L]1 administration, n (%)			
Yes	71 (28.1)	67 (26.9)	0
No	182 (71.9)	182 (73.1)	0
Missing	0	0	101 (100)
Disease status at study entry, n (%)			
Metastatic	226 (89.3)	225 (90.4)	95 (94.1)
Recurrent	27 (10.7)	24 (9.6)	6 (5.9)
Number of prior recurrent/metastatic systemic regimens, n (%)			
1	159 (62.8)	149 (59.8)	71 (70.3)
2	93 (36.8)	100 (40.2)	30 (29.7)
Missing	1 (0.4)	0	0
TF tumor membrane expression prevalence at baseline			
Subjects with evaluable baseline biopsy, n	210	194	80
TF membrane expression ≥1%, n (%)[c]	194 (92.4)	183 (94.3)	77 (96%)

a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

b. Other region includes Latin American countries and Canada.

c. Number of subjects with evaluable biopsy is used as the denominator in computing percentage

n=Number of subjects with evaluable data. Data was not for some subjects because of inadequate tissue quality pr quantity or unavailable tissue.

Data Cutoff Date: SGNTV-003: 24Jul2023, GCT1015-04: 06Feb2020

Primary objective: **ORR**

Table 83 Confirmed Objective Response Rate as Assessed by IRC per RECIST v1.1

	GCT1015-04 (N=101)
Confirmed best objective response	
Complete response	7 (6.9%)
Partial response	17 (16.8%)
Stable disease	49 (48.5%)
Progressive disease	24 (23.8%)
Not evaluable	4 (4.0%)
Confirmed objective response (CR+PR) rate	24 (23.8%)
95% CI[a]	(15.9%; 33.3%)
Confirmed disease control (CR+PR+SD) rate	73 (72.3%)
95% CI[a]	(62.5%; 80.7%)

Data cutoff date: 25-Sep-2020.
Percentages are based on N.
a. Exact 95% two-sided confidence interval using the Clopper-Pearson method.

Secondary objectives: **DOR**

Table 84 Duration of Response as Assessed by IRC per RECIST v.1.1

	GCT1015-04 (N=24)
Duration of response	
Number of events	12 (50.0%)
Number censored	12 (50.0%)
Median DOR (months)	8.5
95% CI	(4.2; NR)
25% quantile DOR (months)	4.2
75% quantile DOR (months)	NR
Range of DOR (months)	1.4+; 19.7+
Kaplan-Meier estimate, % of subjects with DOR ≥6 months	62.4%
95% CI	(36.7%; 80.1%)

Data cutoff date: 25-Sep-2020.
Percentages are based on N.
NR = not reached.
The symbol + indicates a censoring.

OS

Table 85 Summary of OS (SGNTV-003 ITT Analysis Set and GCT1015-04 Full Analysis Set)

	SGNTV-003[a]		GCT1015-04[a]
	Tisotumab Vedotin (N=253)	Chemotherapy[b] (N=249)	Tisotumab Vedotin (N=101)
Number of deaths, n (%)	123 (48.6)	140 (56.2)	58 (57.4)
Subjects censored, n (%)	130 (51.4)	109 (43.8)	43 (42.6)
Stratified hazard ratio[c, d] (95% CI)	0.70 (0.54, 0.89)		
Stratified log-rank p-value[d, e]	0.0038		
Median OS (months) (95% CI)[f]	11.5 (9.8, 14.9)	9.5 (7.9, 10.7)	12.1 (9.6, 13.9)
Q1, Q3	6.7, 21.3	4.6, 16.3	6.9, 16.3
Min, Max[g]	0.4, 25.0	0.0+, 21.9+	0.7, 17.9+
Estimated OS rate at			
6 months (95% CI)[f]	81.4 (75.9, 85.7)	66.9 (60.5, 72.5)	78.7 (69.3, 85.6)
12 months (95% CI)[f]	48.7 (41.0, 55.8)	35.3 (28.0, 42.7)	51.4 (40.9, 60.8)
18 months (95% CI)[f]	33.1 (24.2, 42.2)	23.5 (15.8, 32.2)	- (-, -)

a. SGNTV-003 is a randomized study and GCT1015-04 is a single-arm study.

b. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.

c. Hazard ratio comparing tisotumab vedotin to chemotherapy calculated from the Cox proportional hazards model and Efron method was used in handling ties.

d. Computed using stratification factors [ECOG performance status at baseline: 0 vs 1; Prior bevacizumab administration: yes vs no; Prior anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) administration: yes vs no] at randomization.

e. Two-sided p-value calculated from stratified log-rank test.

f. As estimated using Kaplan-Meier methods and 95% C.I. is calculated using the complimentary log-log transformation method (Collett 1994).

g. '+' means the observed time is from a censored subject.

For SGVTV-003, the threshold for statistical significance is 0.0226 (2-sided).

Data Cutoff Date: SGNTV-003: 24Jul2023, GCT1015-04: 06Feb2020

2.4.5.5.1. Study GEN701 (Expansion Cohorts)

Study design: first-in-human, open-label, multicentre phase 1/2 dose-escalation and expansion safety study
Initiation date: 02-Dec-2013
Completion date: 02-May-2019
Study population: expansion cohorts enrolled across 21 sites (Belgium, Denmark, Sweden, UK and US) with relapsed, advanced, and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, or non-small cell lung cancer who were treated with tisotumab vedotin at the RP2D. A total of **55 subjects with cervical cancer** were enrolled in the expansion part, **50** of whom had r/mCC and ≥1 prior line of therapy in the recurrent or metastatic setting.
Treatment: dose escalation part: dose levels ranging from 0.3 mg/kg to 2.2 mg/kg. The RP2D identified for further evaluation in the **expansion part was 2.0 mg/kg** (up to a maximum of 200 mg for subjects ≥100 kg) administered Q3W. Treatment was given for **4** cycles. Patients showing clinical

benefit, could receive up to a maximum of 8 additional treatment cycles (for **a maximum of 12 cycles** in total).

Efficacy endpoints: ORR and DOR (secondary endpoints) as assessed by an IRC using RECIST v1.1.

Tumour assessments: every 6 weeks during the treatment period (maximum of 12 cycles).

Main inclusion and exclusion criteria:

Eligible subjects were/ had:

- aged 18 years or older;
- advanced or metastatic solid tumours and relapsed after or
- not eligible to receive the available standard of care;
- acceptable organ function, haematological, and coagulation status;
- Eastern Cooperative Oncology Group performance status of 0 or 1;
- measurable disease according to RECIST v.1.1.
- subjects with CRPC, who were clinically refractory or resistant to hormone therapy (as documented by progression), could be included on the basis of their bone metastases or prostate-specific antigen status.

Subjects were excluded if they had:

- current or prior coagulation defects,
- ongoing major bleeding, clinically
- significant cardiac disease,
- major surgery within 6 weeks before tisotumab vedotin infusion or major surgery anticipated during trial treatment,
- had received prior therapy with an auristatin derivative, or
- had received bevacizumab within 12 weeks of the first dose.

Statistical Methods:

A maximum of 48 subjects were expected in the Dose Escalation Part: 3 to 6 subjects per dose level for 8 dose levels. It was estimated that approximately 169 subjects would be enrolled in the Expansion Part. The full analysis set (FAS) was defined as all subjects who had been exposed to tisotumab vedotin in the Dose Escalation Part (FAS1) or in the Expansion Part (FAS2).
No formal statistical testing was done. Ad hoc analyses could be performed as applicable.

Results:

Table 86 Demographic and Baseline Characteristics- Expansion Part

	All Tumors (N=168)	Bladder (N=15)	Cervix (N=55)	Endometrium (N=14)	Esophagus (N=15)	NSCLC (N=15)	Ovary (N=36)	Prostate (N=18)
Sex [n (%)]								
Female	122 (73)	2 (13)	55 (100)	14 (100)	3 (20)	12 (80)	36 (100)	0
Male	46 (27)	13 (87)	0	0	12 (80)	3 (20)	0	18 (100)
Age (years)								
Median	58.0	58.0	46.0	62.5	64.0	60.0	59.0	71.5
Min, Max	21, 79	44, 71	21, 73	48, 67	42, 75	41, 73	40, 75	56, 79
Race [n (%)]								
White	155 (92)	15 (100)	49 (89)	14 (100)	13 (87)	13 (87)	34 (94)	17 (94)
Black or African American	2 (1)	0	1 (2)	0	0	0	0	1 (6)
Asian	5 (3)	0	3 (5)	0	1 (7)	1 (7)	0	0
Native Hawaiian or other Pacific Islander	1 (1)	0	0	0	0	1 (7)	0	0
Other	2 (1)	0	0	0	1 (7)	0	1 (3)	0
Missing	3 (2)	0	2 (4)	0	0	0	1 (3)	0
Ethnicity [n (%)]								
Hispanic or Latino	2 (1)	0	0	1 (7)	0	0	1 (3)	0
Not Hispanic or Latino	164 (98)	15 (100)	53 (96)	13 (93)	15 (100)	15 (100)	35 (97)	18 (100)
Missing	2 (1)	0	2 (4)	0	0	0	0	0
Distant Metastases [n (%)]								
Yes	60 (36)	4 (27)	14 (25)	3 (21)	9 (60)	11 (73)	9 (25)	10 (56)
No	84 (50)	10 (67)	31 (56)	8 (57)	6 (40)	4 (27)	17 (47)	8 (44)
Missing	24 (14)	1 (7)	10 (18)	3 (21)	0	0	10 (28)	0
ECOG Performance Score [n(%)]								
0	68 (41)	11 (73)	21 (38)	7 (50)	3 (20)	1 (7)	19 (54)	6 (33)
1	99 (59)	4 (27)	34 (62)	7 (50)	12 (80)	14 (93)	16 (46)	12 (67)
Missing	1	0	0	0	0	0	1 (3)	0
Time Since Diagnosis of Cancer (months)								
Median	33.5	39.0	23.0	47.5	13.0	19.0	47.0	60.5
Min, Max	3, 194	6, 103	6, 164	7, 194	3, 70	4, 159	9, 162	27, 178

Table 87 Histology Grade by Tumour Type and Most Commonly (>10% or equal) Reported Prior Cancer therapies- Expansion Part)

	All Tumors (N=168)	Bladder (N=15)	Cervix (N=55)	Endometrium (N=14)	Esophagus (N=15)	NSCLC (N=15)	Ovary (N=36)	Prostate (N=18)
Histology grade [n (%)]								
X	39 (23)	5 (33)	9 (16)	2 (14)	5 (33)	3 (20)	7 (19)	8 (44)
1	10 (6)	0	4 (7)	3 (21)	0	0	3 (8)	0
2	25 (15)	2 (13)	15 (27)	3 (21)	2 (13)	1 (7)	2 (6)	0
3	45 (27)	4 (27)	11 (20)	1 (7)	4 (27)	2 (13)	19 (53)	4 (22)
4	30 (18)	0	9 (16)	3 (21)	2 (13)	8 (53)	4 (11)	4 (22)
Missing	19 (11)	4 (27)	7 (13)	2 (14)	2 (13)	1 (7)	1 (3)	2 (11)
Most commonly (≥10%) reported prior cancer therapies (preferred term) [n (%)]								
Carboplatin	105 (63)	1 (7)	41 (75)	14 (100)	4 (27)	10 (67)	35 (97)	0
Paclitaxel	103 (61)	1 (7)	50 (91)	12 (86)	4 (27)	3 (20)	33 (92)	0
Radiotherapy	88 (52)	5 (33)	42 (76)	10 (71)	7 (47)	7 (47)	4 (11)	13 (72)
Cisplatin	79 (47)	11 (73)	44 (80)	1 (7)	9 (60)	10 (67)	4 (11)	0
Bevacizumab	55 (33)	0	40 (73)	0	0	1 (7)	14 (39)	0
Gemcitabine	40 (24)	11 (73)	5 (9)	1 (7)	0	4 (27)	19 (53)	0
Docetaxel	36 (21)	1 (7)	2 (4)	1 (7)	5 (33)	5 (33)	4 (11)	18 (100)
Topotecan	18 (11)	0	13 (24)	2 (14)	0	0	3 (8)	0

ORR

Table 88 Confirmed Objective Response Rate per RECIST v1.1 (Investigator and IRC Assessment) by Tumours type- Expansion Part

Best overall response and objective response rate	All Tumors (N=168)	Bladder (N=15)	Cervix (N=55)	Cervix (N=50)[a]	Endometrium (N=14)	Esophagus (N=15)	NSCLC (N=15)	Ovary (N=36)	Prostate (N=18)
IRC assessment									
CR – n (%)	3 (2)	0	1 (2)	1 (2)	0	0	0	2 (6)	0
PR – n (%)	22 (13)	3 (20)	11 (20)	10 (20)	1 (7)	2 (13)	2 (13)	3 (8)	0
SD – n (%)	77 (46)	5 (33)	21 (38)	19 (38)	8 (57)	3 (20)	7 (47)	21 (58)	12 (67)
PD – n (%)	44 (26)	5 (33)	17 (31)	16 (32)	3 (21)	6 (40)	3 (20)	6 (17)	4 (22)
NE – n (%)	22 (13)	2 (13)	5 (9)	4 (8)	2 (14)	4 (27)	3 (20)	4 (11)	2 (11)
Objective Response Rate – n (%) [95% CI]	25 (15) [10, 21]	3 (20) [4, 48]	12 (22) [12, 35]	11 (22) [12, 36]	1 (7) [0, 34]	2 (13) [2, 40]	2 (13) [2, 40]	5 (14) [5, 29]	0 [0, 19]
Investigator assessment									
CR – n (%)	0	0	0	0	0	0	0	0	0
PR – n (%)	27 (16)	4 (27)	13 (24)	11 (22)	1 (7)	2 (13)	2 (13)	5 (14)	0
SD – n (%)	74 (44)	3 (20)	20 (36)	19 (38)	8 (57)	4 (27)	7 (47)	21 (58)	11 (61)
PD – n (%)	47 (28)	7 (47)	18 (33)	17 (34)	3 (21)	5 (33)	4 (27)	6 (17)	4 (22)
NE – n (%)	20 (12)	1 (7)	4 (7)	3 (6)	2 (14)	4 (27)	2 (13)	4 (11)	3 (17)
Objective Response Rate – n (%) [95% CI]	27 (16) [11, 23]	4 (27) [8, 55]	13 (24) [13, 37]	11 (22) [12, 36]	1 (7) [0, 34]	2 (13) [2, 40]	2 (13) [2, 40]	5 (14) [5, 29]	0 [0, 19]

95% CIs were calculated using the Clopper-Pearson method.
A responder was defined as any subject with a best overall response of CR or PR.
CI, confidence interval; CR, complete response; IRC, independent review committee; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
a: Ad hoc analyses conducted on a subset of the cervical cancer cohort, where prior therapy could be confirmed (Section 9.8.2).

DOR (table not shown): median DOR by IRC was 5.1 months (95%CI: 3.0, 9.7) and median DOR by Inv was 5.6 months (95%CI: 3.0,9.6).

2.4.6. Discussion on clinical efficacy

Based on the results of the pivotal trial SGNTV-003 (innovaTV301), the applicant applied for following indication:

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

Design and conduct of clinical studies

During clinical development of tisotumab vedotin, scientific advices were given, the most relevant SA regarding design of the pivotal study in 2019 (EMEA/H/SA/4115/1/2019/III). The applicant complied with CHMP advice given on selection of the primary endpoint and application of ITT principle in the statistical plan, yet some of the recommendations, such as a stratification by the type of doublet chemotherapy (platinum vs. non-platinum), sufficient representations of platinum-naïve/platinum exposed subgroups, addition of BICR for assessment of PFS, were not considered.

Based on favourable efficacy and safety results from phase I GEN701 and phase II GCT1015-04 trials, SGNTV-003 (innovaTV301) was designed as an open-label phase III RCT to evaluate tisotumab vedotin in comparison to one of five chemotherapy choices (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in the 2L+ setting of recurrent\metastatic cervical cancer.

The design of the trial had been discussed with the CHMP before starting recruitment (SA dated May 2019). The applicant complied with CHMP advice given on selection of the primary endpoint and application of the ITT principle in the statistical plan, yet some of the recommendations, such as a stratification by the type of doublet chemotherapy (platinum vs. non-platinum), sufficient representations of platinum-naïve/platinum exposed subgroups, addition of BICR for assessment of PFS, were not considered for study design and conduct.

Inclusion and exclusion criteria did not suffer major changes along protocol amendments during the recruitment period. Although most patients received platinum-based therapy as previous line of therapy (see baseline characteristics), prior platinum therapy is not expected to be an effect modifier. Benefit may also be expected in patients who are platinum-ineligible, but their overall health status (e.g., co-morbidities) should be taken into account. This is, however, an individual benefit-risk balance that should be made by the patient and their treating physician.

Statistical methods: OS as the primary endpoint for the pivotal trial represents a relevant and objective measure of clinical benefit. No crossover between treatment arms was allowed, strengthening the objectiveness of the primary endpoint. Secondary endpoints were PFS, ORR, TTR and DOR assessed by the Investigator. During the scientific advice, the CHMP recommended the implementation of an independent central review to validate the secondary endpoints, including PFS. This approach would have bolstered confidence in the outcomes of the open-label study. However, this might be partially mitigated by the fact that OS was the primary endpoint. Using the ITT for OS, PFS and ORR analyses is supported**.** Time-to-tumour-response (TTR) and DOR were assessed only among confirmed responders from the ITT population, and this approach is acceptable. The randomisation procedure was appropriate and the stratification factors (ECOG PS, prior bevacizumab, prior anti PD(L)1 therapy and region) are clinically relevant. OS in the pivotal trial was analysed using a stratified Cox proportional hazards regression model, controlling for all randomisation stratification factors except for region. An explanation for excluding region as a confounder due to concerns about sparse

strata was provided. Four sensitivity analyses were planned to ensure the robustness of the OS results, but only two were performed. A Restricted mean survival time (RMST) analysis and results were provided, as the Log-Negative-Log of Survival vs. Log (Time) Plot, the Schoenfeld Residuals Plot, and the Kaplan-Meier Survival Curves all suggested a potential violation of the PH assumption for OS. The confidence interval does not cross zero, indicating a statistically significant difference between the treatment arms, further supporting the robustness of the findings. The strategies implemented to control type I error along hierarchical testing are appropriate. Given that ORR did not meet the anticipated boundary of 25% (it was ~18%), clarification was provided on how the lower-than-expected ORR affects the ability to test DOR and TTR. The response indicated that no adjustments were needed and clarified the supportive, rather than confirmatory, role of DOR and TTR in the overall analysis.

Results: 502 patients were randomised in the recruitment period: 253 to the tisotumab vedotin arm and the remainder to chemotherapy (investigator's predefined choice of topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed). The slightly higher proportion of discontinuations because of subject or physician decision in the control arm is anticipated in an open-label trial. Most common screen failures were due to organ functioning, ECOG status and non-measurable disease. These screen failures indicate that the study population was likely medically fitter compared to the overall target population.

Overall, baseline demographic and disease characteristics of patients from Study SGNTV-003 are balanced between both arms of treatment, and are consistent with inclusion/exclusion criteria, reflecting the targeted population for treatment with tisotumab vedotin. Nearly all of patients (98.8% of study population) received prior platinum-based therapy. The proportion of tumours with squamous and adenocarcinoma/adenosquamous histology in patients from the study reflects the global distribution of cervical cancer histologies.

Efficacy data and additional analyses

At data cutoff of 24-July-2023 and with a median follow-up of 10.8 months, 263 deaths had occurred (52% of OS maturity) in the ITT population of SGNTV-003. The study met its primary endpoint, HR for OS showed statistically significant superiority of tisotumab vedotin over chemotherapy: 0.70 (95% CI 0.54, 0.89), p-value 0.0038. K-M estimates of median OS were 11.5 months in the tisotumab vedotin arm and 9.5 months in the chemotherapy arm. Regardless of this discrete improved performance of the control arm in SGNTV-003, tisotumab vedotin still showed a statistically significant improvement over chemotherapy, noting the unmet medical need for improved outcomes in patients who progressed on/after immune checkpoint inhibitors. Due to the early interim analysis for OS, there is a considerable rate of censoring across both curves. However, most of the censoring was for administrative reasons (i.e., last known alive date within 30 days of the data cutoff). The remaining participants were censored due to withdrawal of consent, except for one participant who was censored due to loss of follow-up. As expected, withdrawal of consent occurred more frequently in the chemotherapy arm compared to the tisotumab vedotin arm (8 participants vs 5 participants, respectively). It is assumed that this issue had a negligible impact on OS results.

At 78% of PFS events, HR for PFS by INV was 0.67 (95% CI 0.54, 0.82), p-value <0.0001. K-M estimates of median PFS were 4.2 months in the tisotumab vedotin arm and 2.9 in the chemotherapy arm. The PFS results for the comparator arm are in line with historical data.(Study 1676 (Tewari 2022)).

ORR by investigator in the ITT population was also statistically significantly improved (17.8% vs. 5.2%, Odds Ratio 4.0, p-value <0.0001) in the tisotumab vedotin compared to the chemotherapy arm. The majority of patients in the tisotumab vedotin arm had stable disease (SD) as the best overall

response, albeit 6 durable complete responses were observed, which is not expected in this disease setting. The median TTR for the confirmed responders was 1.58 and 1.74 months in the tisotumab vedotin and chemotherapy arms, respectively. Median DOR was 5.3 (95%CI: 4.2,8.3) and 5.7 months (95%CI: 2.8, -) in the tisotumab vedotin vs. chemotherapy arm, respectively. Around 50% of the total study population received subsequent anti-cancer therapy within ~6 weeks from the last dose of study drug. A slightly higher proportion of patients in the tisotumab vedotin arm (44.3% vs. 36.5%) received systemic therapy as the subsequent treatment. The most common subsequent systemic treatment for both arms was chemotherapy (73.2 % and 62.6% of patients in Tivdak and chemotherapy arm, respectively). The utility of immunotherapy was well-balanced across treatment arms. This is reassuring and strengthens the validity of observed OS benefit with Tivdak. Moreover, this could also explain the improved performance of chemotherapy arm in comparison to the historical data.

In conclusion, OS and PFS benefits were observed from treatment with tisotumab vedotin compared to the investigator's choice of chemotherapy. The results are clinically meaningful in the setting of 2L+ line of recurrent\metastatic cervical cancer.

Subgroup analyses supported an OS benefit of tisotumab vedotin compared with chemotherapy across nearly all prespecified subgroups with the exception of prior bevacizumab exposure [HR 1.0 (95% CI 0.66, 1.5) in patients who had not received bevacizumab]. A literature search found no biologic rationale that could explain such subgroup results. In innovaTV301, the KM curves for OS for patients with/without prior bevacizumab exposure were provided. Looking at the OS curves for the patients without prior bevacizumab, while the effect does appear to be weaker compared with the group with prior bevacizumab, there is an indication that the curves were starting to separate in favour of the tisotumab vedotin arm before a heavy censoring cluster. Moreover, the lack of a biological rationale and inconsistency across clinical trials make the subgroup results less credible. As a result, it is unlikely that there is a differential treatment effect in relation to the prior bevacizumab exposure.

For the vinorelbine subgroup the observed OS benefit (HR 1.19 [95% CI: 0.41, 3.46]) might have been affected by the timing of analysis and update of results was requested. The updated results were consistent with the primary results with HR over 1 and wide CI. However, the small sample size of this subgroup prevents from drawing any conclusion.

Subgroup analyses of secondary endpoints (PFS, ORR) confirmed a consistent treatment effect for tisotumab vedotin compared to chemotherapy across all prespecified subgroups.

Of the 253 patients in the tisotumab vedotin arm, 210 had an evaluable biopsy for TF expression. Of those, 92% had TF membrane expression ≥ 1% and 88.6 % had TF cytoplasmic expression ≥1%. Median membrane H-score was 45 (range 0-291) and median percentage of tumour cells positive for membrane TF expression was 25% (range 0-100%). Among patients with confirmed best overall response (N=200) wide range of membrane H-scores were observed. Similar results were seen when TF expression was based on cytoplasm staining. Based on these results, there does not seem to be a clear correlation between TF expression and efficacy of tisotumab vedotin in terms of ORR. OS benefit is observed across the entire range of H-scores, noticing seemingly greater benefit with higher scores, both for cytoplasmic and membrane expressions. HRs for patients with lower H-scores (membrane and cytoplasmic) were consistent with the HR for the ITT population, which is reassuring. Similarly, PFS results indicated efficacy of tisotumab vedotin regardless of H-score of TF expression on cell's membrane or in the cytoplasm. Limited data exist to consider restricting the indication to the population with TF membrane expression >1%.

Relevant questionnaires for assessing PROs were used, however completion of those were voluntary. Using PROs is acknowledged, nevertheless the open-label design of the study and use of descriptive

statistics compromises interpretation of their results. Overall, QoL of patients in the tisotumab vedotin arm seemed to be maintained during the study.

As supportive data, the applicant submitted efficacy results from advanced cervical cancer cohorts of phase I (GEN-701) and phase II (GCT1015-04) trials along the clinical development of tisotumab vedotin. Overall, results from study GCT1015-04 are consistent with those from pivotal trial SGNTV-003 and support efficacy of tisotumab vedotin in the treatment of 2L+ recurrent/metastatic cervical cancer. It is acknowledged that the applicant provided efficacy results from the FIH phase 1/2 study GEN 701 to support the proposed indication.

The proposed indication is agreed and refers to the section 5.1 of SmPc for specification of the studied population.

Additional expert consultation

The comments from the European Organisation for Research and Treatment of Cancer (EORTC) and the patients' organisations Olijf and Gynca with regards to tisotumab vedotin were received. Both organisations have emphasised the need for more efficacious therapies for the recurrent/metastatic cervical cancer, but novel treatments should not have a negative impact on the quality of life of patients. These statements are of high importance and are taken into consideration. Since descriptive statistics were used and filling out the PRO questionnaires was voluntary during the tisotumab vedotin clinical development program, the relevance of their findings in the benefit/risk assessment is considered limited.

2.4.7. Conclusions on the clinical efficacy

The primary analysis of study SGNTV-003 (innovaTV301) showed statistically significant and clinically relevant improvements in survival from tisotumab vedotin over investigator's choice of chemotherapy in the 2L+ setting of recurrent/metastatic cervical cancer. In addition, benefit of tisotumab vedotin over chemotherapy is observed across Investigator-assessed secondary endpoints as PFS and ORR. The favourable effects are considered clinically meaningful.

2.4.8. Clinical safety

The safety population comprises 628 subjects (including 250 subjects from the tisotumab vedotin arm of SGNTV-003) dosed with tisotumab vedotin monotherapy across 7 studies and 239 subjects dosed in the chemotherapy arm of SGNTV-003. All subjects treated with tisotumab vedotin received the recommended dose of 2.0 mg/kg Q3W. The 4 safety analysis groups are described in Table 93.

Table 89 Integrated Safety Analysis Groups

Safety Analysis Group	Patient Population	Studies Included	Total Number of Subjects Included
SGNTV-003 Pivotal Cervical Cancer[a]	Subjects with cervical cancer who received 2.0 mg/kg Q3W tisotumab vedotin monotherapy or chemotherapy	SGNTV-003	489 Tisotumab vedotin n=250 Chemotherapy n=239
GCT1015-04 Supportive Cervical Cancer	Subjects with cervical cancer who received 2.0 mg/kg Q3W tisotumab vedotin monotherapy in GCT1015-04	GCT1015-04	101
Pool 1	All subjects with cervical cancer who received	SGNTV-003 (TV arm), GCT1015-04, GEN701	425[b]

All Cervical Cancer[b]	2.0 mg/kg Q3W tisotumab vedotin monotherapy	(Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion)	
Pool 2 All Tumour Types[c]	Subjects with any tumour type who received 2.0 mg/kg Q3W tisotumab vedotin monotherapy	SGNTV-003 (TV arm), GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).	628[c]

a. The safety data from SGNTV-003 will be based on the SGNTV-003 safety analysis set, which consists of subjects who are randomised on or before the date of the last patient in (LPI) in the global study and receive any amount of study treatment (tisotumab vedotin or chemotherapy).
b. Studies SGNTV-003 (TV arm) n=250, GCT1015-04 n=101, GEN701 (Cohort Expansion) n=54, GEN702 (Cohort Expansion) n=3, GCT1015-03 subjects with cervical cancer n=2 (counted in GEN701 and GEN 702 totals), and GCT1015-06 (Cohort Expansion) n=17.
c. Studies SGNTV-003 (TV arm) n=250, GEN701 (Cohort Expansion) n=167, GEN702 (Cohort Expansion) n=4, GCT1015-03 n=4 (counted in GEN701 and GEN 702 totals), GCT1015-04 n=101, GCT1015-06 (Cohort Expansion) n=17, and SGNTV-001 (Part A) n=89.

2.4.8.1. Patient exposure

Table 90 Summary of Extent of Study Treatment Exposure (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumour Types) (N=628)
Duration of study treatment [d] (months)					
N	250	239	101	425	628
Mean (STD)	4.28 (2.74)	3.47 (2.86)	5.08 (5.10)	4.36 (3.46)	3.85 (3.25)
Median	3.65	2.76	4.24	3.68	3.02
Min, Max	0.4, 18.9	0.1, 20.9	0.7, 40.2	0.4, 40.2	0.3, 40.2
Number of cycles [e] received					
N	250	239	101	425	628
Mean (STD)	5.8 (3.6)	4.8 (3.9)	6.9 (6.9)	5.9 (4.6)	5.3 (4.3)
Median	5.0	4.0	6.0	5.0	4.0
Min, Max	1, 26	1, 30	1, 56	1, 56	1, 56
Actual cumulative TV dose (mg/kg)					
N	250	NA	101	425	628
Mean (STD)	10.59 (5.93)	NA	12.40 (10.11)	10.84 (7.29)	9.63 (6.92)
Median	10.00	NA	10.71	10.00	8.00
Min, Max	2.0, 30.1	NA	2.0, 77.9	1.1, 77.9	1.1, 77.9
Relative TV dose intensity[f] (%)					
N	250	NA	101	425	628
Mean (STD)	89.31 (14.11)	NA	90.64 (12.98)	90.07 (13.49)	90.74 (13.16)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumour Types) (N=628)
Median	96.09	NA	95.93	96.33	97.53
Min, Max	46.5, 107.7	NA	43.8, 113.9	43.8, 113.9	43.8, 113.9

NA = Not Applicable; STD= standard deviation.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. Duration of study treatment (months) = (end of study treatment - first dose date of study treatment + 1) / 30.4375. End of study treatment is defined as in SAP Section 2.2.
e. Cycle with any amount (>0) of study treatment received.
f. Relative dose intensity = actual dose intensity / intended dose intensity (IDI) * 100%, where IDI is 2.0 mg/kg/3weeks.
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

2.4.8.1. Adverse events

Table 91 Summary of Disposition (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects who received at least one dose of study treatment	250 (100)	239 (100)	101 (100)	425 (100)	628 (100)
Subjects on study treatment	21 (8.4)	16 (6.7)	0	21 (4.9)	21 (3.3)
Subjects off study treatment	229 (91.6)	223 (93.3)	101 (100)	404 (95.1)	607 (96.7)
Reason for treatment discontinuation					
Progressive disease[e]	177 (70.8)	193 (80.8)	76 (75.2)	308 (72.5)	434 (69.1)
Adverse event	40 (16.0)	9 (3.8)	15 (14.9)	66 (15.5)	103 (16.4)
Investigator decision	2 (0.8)	3 (1.3)	1 (1.0)	4 (0.9)	21 (3.3)
Subject decision, non-AE / Withdraw of consent	8 (3.2)	17 (7.1)	5 (5.0)	16 (3.8)	36 (5.7)
Death[f]	0	0	4 (4.0)	4 (0.9)	4 (0.6)
Other, non-AE / Lost to follow-up	2 (0.8)	1 (0.4)	0	3 (0.7)	4 (0.6)
Study termination by sponsor	0	0	0	0	0
Missing [d]	0	0	0	3 (0.7)	5 (0.8)

a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. The 5 missing in Pool 2 are subjects who completed treatment in GEN701: 4 subjects continued treatment in GCT1015-03 and reasons for treatment discontinuation are not collected in GCT1015-03; 1 subject did not continue treatment in GCT1015-03.
e. Includes both radiographic disease progression and clinical progression.

f. Not applicable to SGNTV-003 and SGNTV-001. The primary causes of death for the 4 treatment discontinuations due to death in GCT1015-04 were deterioration of underlying cancer disease (n=1), adverse event (n=2) and other (n=1).

Table 92 Summary of TEAEs (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any TEAE	246 (98.4)	237 (99.2)	101 (100)	421 (99.1)	620 (98.7)
Treatment-related TEAE[d]	219 (87.6)	204 (85.4)	93 (92.1)	385 (90.6)	565 (90.0)
Subjects with ≥ Grade 3 TEAE	130 (52.0)	149 (62.3)	62 (61.4)	236 (55.5)	351 (55.9)
≥ Grade 3 treatment-related TEAE	73 (29.2)	108 (45.2)	29 (28.7)	131 (30.8)	199 (31.7)
Subjects with any TE SAE	82 (32.8)	94 (39.3)	44 (43.6)	159 (37.4)	243 (38.7)
Treatment-related TE SAE	26 (10.4)	35 (14.6)	14 (13.9)	57 (13.4)	94 (15.0)
Subjects with TEAE leading to permanent treatment discontinuation	37 (14.8)	9 (3.8)	14 (13.9)	64 (15.1)	114 (18.2)
Treatment-related TEAE leading to permanent treatment discontinuation	34 (13.6)	4 (1.7)	13 (12.9)	60 (14.1)	108 (17.2)
Subjects with Grade 5 TEAE	4 (1.6)	5 (2.1)	4 (4.0)	8 (1.9)	10 (1.6)
Treatment-related Grade 5 TEAE	2 (0.8)	1 (0.4)	1 (1.0)	3 (0.7)	3 (0.5)

TE SAE = Treatment-emergent serious adverse events.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. Related to study treatment as assessed by the investigator.
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023
Source: SGNTV-003 ISS, Table 10.5.1

Table 93 TEAEs with Incidence ⩾10% in SGNTV-003 tisotumab vedotin or Chemotherapy Arm by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	246 (98.4)	237 (99.2)	101 (100)	421 (99.1)	620 (98.7)
Nausea	83 (33.2)	96 (40.2)	41 (40.6)	159 (37.4)	254 (40.4)
Conjunctivitis	78 (31.2)	1 (0.4)	31 (30.7)	136 (32.0)	200 (31.8)
Peripheral sensory neuropathy	71 (28.4)	6 (2.5)	19 (18.8)	99 (23.3)	130 (20.7)

Preferred Term	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250) n (%)	SGNTV-003 (Pivotal Cervical) Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Epistaxis	65 (26.0)	6 (2.5)	39 (38.6)	142 (33.4)	252 (40.1)
Constipation	62 (24.8)	39 (16.3)	22 (21.8)	104 (24.5)	177 (28.2)
Alopecia	61 (24.4)	7 (2.9)	39 (38.6)	132 (31.1)	200 (31.8)
Decreased appetite	59 (23.6)	42 (17.6)	18 (17.8)	99 (23.3)	173 (27.5)
Anaemia	58 (23.2)	125 (52.3)	34 (33.7)	115 (27.1)	143 (22.8)
Diarrhoea	54 (21.6)	36 (15.1)	25 (24.8)	104 (24.5)	166 (26.4)
Vomiting	44 (17.6)	44 (18.4)	18 (17.8)	84 (19.8)	139 (22.1)
Pyrexia	42 (16.8)	50 (20.9)	17 (16.8)	73 (17.2)	94 (15.0)
Asthenia	40 (16.0)	38 (15.9)	19 (18.8)	60 (14.1)	79 (12.6)
Keratitis	39 (15.6)	0	11 (10.9)	53 (12.5)	61 (9.7)
Abdominal pain	34 (13.6)	23 (9.6)	14 (13.9)	63 (14.8)	103 (16.4)
Dry eye	33 (13.2)	1 (0.4)	25 (24.8)	73 (17.2)	122 (19.4)
Urinary tract infection	33 (13.2)	38 (15.9)	12 (11.9)	57 (13.4)	67 (10.7)
Fatigue	32 (12.8)	39 (16.3)	35 (34.7)	99 (23.3)	197 (31.4)
Pruritus	25 (10.0)	7 (2.9)	14 (13.9)	49 (11.5)	71 (11.3)
Vaginal haemorrhage	25 (10.0)	13 (5.4)	12 (11.9)	43 (10.1)	46 (7.3)
Alanine aminotransferase increased	18 (7.2)	26 (10.9)	1 (1.0)	29 (6.8)	40 (6.4)
Aspartate aminotransferase increased	17 (6.8)	27 (11.3)	1 (1.0)	27 (6.4)	44 (7.0)
Neutropenia	17 (6.8)	54 (22.6)	4 (4.0)	24 (5.6)	37 (5.9)
Oedema peripheral	9 (3.6)	30 (12.6)	8 (7.9)	21 (4.9)	36 (5.7)

Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 94 TEAEs ⩾ Grade 3 Reported in ⩾2% of Subjects in the SGNTV-003 tisotumab vedotin or Chemotherapy Arm by PT (Integrated Safety Analysis Set)

Preferred Term	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250) n (%)	SGNTV-003 (Pivotal Cervical) Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	130 (52.0)	149 (62.3)	62 (61.4)	236 (55.5)	351 (55.9)
Anaemia	21 (8.4)	66 (27.6)	8 (7.9)	42 (9.9)	53 (8.4)

Preferred Term	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250) n (%)	SGNTV-003 (Pivotal Cervical) Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Urinary tract infection	11 (4.4)	17 (7.1)	3 (3.0)	15 (3.5)	18 (2.9)
Abdominal pain	10 (4.0)	4 (1.7)	1 (1.0)	14 (3.3)	23 (3.7)
Fatigue	9 (3.6)	10 (4.2)	6 (5.9)	21 (4.9)	36 (5.7)
Neutropenia	9 (3.6)	32 (13.4)	3 (3.0)	12 (2.8)	18 (2.9)
Peripheral sensory neuropathy	7 (2.8)	0	2 (2.0)	10 (2.4)	15 (2.4)
Small intestinal obstruction	6 (2.4)	1 (0.4)	0	6 (1.4)	10 (1.6)
Asthenia	5 (2.0)	5 (2.1)	2 (2.0)	7 (1.6)	12 (1.9)
Keratitis	5 (2.0)	0	0	5 (1.2)	6 (1.0)
Sepsis	5 (2.0)	2 (0.8)	0	5 (1.2)	10 (1.6)
Alanine aminotransferase increased	4 (1.6)	5 (2.1)	0	5 (1.2)	7 (1.1)
Hypertension	4 (1.6)	5 (2.1)	1 (1.0)	6 (1.4)	9 (1.4)
Hypokalaemia	4 (1.6)	5 (2.1)	2 (2.0)	9 (2.1)	15 (2.4)
Acute kidney injury	3 (1.2)	5 (2.1)	1 (1.0)	4 (0.9)	5 (0.8)
Febrile neutropenia	2 (0.8)	9 (3.8)	0	3 (0.7)	6 (1.0)
Hydronephrosis	2 (0.8)	6 (2.5)	0	3 (0.7)	4 (0.6)
Hypophosphataemia	1 (0.4)	5 (2.1)	0	2 (0.5)	4 (0.6)
Nausea	1 (0.4)	5 (2.1)	0	5 (1.2)	7 (1.1)
Leukopenia	0	7 (2.9)	0	0	0
Neutrophil count decreased	0	11 (4.6)	0	1 (0.2)	2 (0.3)
Oedema peripheral	0	5 (2.1)	0	0	0
Platelet count decreased	0	5 (2.1)	1 (1.0)	2 (0.5)	2 (0.3)
Thrombocytopenia	0	5 (2.1)	0	0	0

Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 95 Treatment-Related TEAEs Reported in ⩾5% of Subjects in the SGNTV-003 tisotumab vedotin or Chemotherapy Arm by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	219 (87.6)	204 (85.4)	93 (92.1)	385 (90.6)	565 (90.0)
Conjunctivitis	76 (30.4)	1 (0.4)	26 (25.7)	129 (30.4)	192 (30.6)
Nausea	73 (29.2)	86 (36.0)	27 (26.7)	127 (29.9)	202 (32.2)
Peripheral sensory neuropathy	67 (26.8)	5 (2.1)	15 (14.9)	90 (21.2)	119 (18.9)
Alopecia	61 (24.4)	7 (2.9)	38 (37.6)	129 (30.4)	196 (31.2)
Epistaxis	57 (22.8)	5 (2.1)	30 (29.7)	122 (28.7)	221 (35.2)
Decreased appetite	45 (18.0)	24 (10.0)	11 (10.9)	74 (17.4)	132 (21.0)
Diarrhoea	40 (16.0)	21 (8.8)	9 (8.9)	70 (16.5)	107 (17.0)
Keratitis	39 (15.6)	0	11 (10.9)	53 (12.5)	61 (9.7)
Asthenia	35 (14.0)	31 (13.0)	13 (12.9)	49 (11.5)	61 (9.7)
Vomiting	34 (13.6)	35 (14.6)	10 (9.9)	60 (14.1)	100 (15.9)
Dry eye	33 (13.2)	1 (0.4)	23 (22.8)	71 (16.7)	117 (18.6)
Anaemia	32 (12.8)	105 (43.9)	13 (12.9)	61 (14.4)	79 (12.6)
Constipation	29 (11.6)	20 (8.4)	9 (8.9)	46 (10.8)	73 (11.6)
Fatigue	28 (11.2)	30 (12.6)	26 (25.7)	81 (19.1)	168 (26.8)
Pyrexia	26 (10.4)	20 (8.4)	7 (6.9)	39 (9.2)	53 (8.4)
Pruritus	21 (8.4)	5 (2.1)	11 (10.9)	40 (9.4)	60 (9.6)
Alanine aminotransferase increased	17 (6.8)	20 (8.4)	1 (1.0)	27 (6.4)	33 (5.3)
Neutropenia	16 (6.4)	52 (21.8)	4 (4.0)	22 (5.2)	34 (5.4)
Weight decreased	15 (6.0)	6 (2.5)	6 (5.9)	26 (6.1)	49 (7.8)
Aspartate aminotransferase increased	14 (5.6)	19 (7.9)	1 (1.0)	23 (5.4)	34 (5.4)
Leukopenia	3 (1.2)	15 (6.3)	1 (1.0)	4 (0.9)	7 (1.1)
Neutrophil count decreased	2 (0.8)	20 (8.4)	2 (2.0)	7 (1.6)	9 (1.4)
Platelet count decreased	0	12 (5.0)	2 (2.0)	3 (0.7)	5 (0.8)
Thrombocytopenia	0	13 (5.4)	1 (1.0)	1 (0.2)	1 (0.2)

Related to study treatment as assessed by the investigator.
Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 96. Treatment-Related Treatmen-emergency Grade 3 or higher adverse event by Preferred Term SGNTV-003 Safety Analysis Set

			Chemotherapy				
Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy (N=239) n (%)	Topotecan (N=19) n (%)	Vinorelbine (N=17) n (%)	Gemcitabine (N=109) n (%)	Irinotecan (N=14) n (%)	Pemetrexed (N=80) n (%)
Subjects with any event	73 (29.2)	108 (45.2)	7 (36.8)	8 (47.1)	52 (47.7)	10 (71.4)	31 (38.8)
Anaemia	9 (3.6)	52 (21.8)	5 (26.3)	1 (5.9)	23 (21.1)	4 (28.6)	19 (23.8)
Fatigue	9 (3.6)	6 (2.5)	1 (5.3)	0	3 (2.8)	0	2 (2.5)
Neutropenia	9 (3.6)	31 (13.0)	0	7 (41.2)	17 (15.6)	2 (14.3)	5 (6.3)
Peripheral sensory neuropathy	7 (2.8)	0	0	0	0	0	0
Keratitis	5 (2.0)	0	0	0	0	0	0
Asthenia	4 (1.6)	3 (1.3)	0	0	0	0	3 (3.8)
Diarrhoea	4 (1.6)	3 (1.3)	0	0	0	3 (21.4)	0
Alanine aminotransferase increased	3 (1.2)	5 (2.1)	0	0	4 (3.7)	0	1 (1.3)
Hypertransaminasaemia	3 (1.2)	0	0	0	0	0	0
Vomiting	3 (1.2)	0	0	0	0	0	0
Febrile neutropenia	2 (0.8)	8 (3.3)	1 (5.3)	2 (11.8)	0	2 (14.3)	3 (3.8)
Gait disturbance	2 (0.8)	0	0	0	0	0	0
Hepatic cytolysis	2 (0.8)	0	0	0	0	0	0
Hyponatraemia	2 (0.8)	0	0	0	0	0	0
Muscular weakness	2 (0.8)	0	0	0	0	0	0
Peripheral sensorimotor neuropathy	2 (0.8)	0	0	0	0	0	0
Stevens-Johnson syndrome	2 (0.8)	1 (0.4)	0	0	1 (0.9)	0	0
Ulcerative keratitis	2 (0.8)	0	0	0	0	0	0
Abdominal pain	1 (0.4)	0	0	0	0	0	0
Activated partial thromboplastin time prolonged	1 (0.4)	0	0	0	0	0	0
Acute kidney injury	1 (0.4)	1 (0.4)	0	0	1 (0.9)	0	0
Blood creatinine increased	1 (0.4)	0	0	0	0	0	0
Colitis	1 (0.4)	0	0	0	0	0	0
Corneal degeneration	1 (0.4)	0	0	0	0	0	0
Decreased appetite	1 (0.4)	1 (0.4)	0	0	1 (0.9)	0	0
Enteritis	1 (0.4)	0	0	0	0	0	0
Enterocolitis infectious	1 (0.4)	0	0	0	0	0	0
Erythema	1 (0.4)	0	0	0	0	0	0
Gastrointestinal toxicity	1 (0.4)	0	0	0	0	0	0
General physical health deterioration	1 (0.4)	0	0	0	0	0	0
Haemorrhage	1 (0.4)	0	0	0	0	0	0
Hepatic function abnormal	1 (0.4)	0	0	0	0	0	0
Hyperglycaemia	1 (0.4)	0	0	0	0	0	0
Hypokalaemia	1 (0.4)	2 (0.8)	0	0	1 (0.9)	0	1 (1.3)
Iron deficiency anaemia	1 (0.4)	0	0	0	0	0	0
Large intestinal obstruction	1 (0.4)	0	0	0	0	0	0
Liver injury	1 (0.4)	0	0	0	0	0	0
Lymphopenia	1 (0.4)	2 (0.8)	0	0	2 (1.8)	0	0
Myalgia	1 (0.4)	0	0	0	0	0	0

Nasal congestion	1 (0.4)	0	0	0	0	0	0
Nausea	1 (0.4)	3 (1.3)	0	0	1 (0.9)	1 (7.1)	1 (1.3)
Neuralgia	1 (0.4)	0	0	0	0	0	0
Proctitis	1 (0.4)	1 (0.4)	0	0	0	0	1 (1.3)
Pruritus	1 (0.4)	0	0	0	0	0	0
Punctate keratitis	1 (0.4)	0	0	0	0	0	0
Rash erythematous	1 (0.4)	0	0	0	0	0	0
Rash macular	1 (0.4)	1 (0.4)	0	0	0	0	1 (1.3)
Rash maculo-papular	1 (0.4)	1 (0.4)	0	0	1 (0.9)	0	0
Salivary gland disorder	1 (0.4)	0	0	0	0	0	0
Urinary tract infection	1 (0.4)	3 (1.3)	0	0	0	1 (7.1)	2 (2.5)
Vaginal haemorrhage	1 (0.4)	0	0	0	0	0	0
Weight decreased	1 (0.4)	0	0	0	0	0	0
White blood cell count decreased	1 (0.4)	4 (1.7)	0	0	2 (1.8)	1 (7.1)	1 (1.3)
Abdominal pain upper	0	1 (0.4)	0	0	0	1 (7.1)	0
Aspartate aminotransferase increased	0	2 (0.8)	0	0	1 (0.9)	0	1 (1.3)
Bilirubin conjugated increased	0	1 (0.4)	0	0	0	0	1 (1.3)
C-reactive protein increased	0	1 (0.4)	0	0	0	0	1 (1.3)
Cellulitis	0	2 (0.8)	0	0	1 (0.9)	0	1 (1.3)
Cystitis	0	1 (0.4)	0	0	0	0	1 (1.3)
Dehydration	0	2 (0.8)	0	0	1 (0.9)	1 (7.1)	0
Dermatitis acneiform	0	1 (0.4)	0	0	0	0	1 (1.3)
Drug reaction with eosinophilia and systemic symptoms	0	1 (0.4)	0	0	1 (0.9)	0	0
Febrile bone marrow aplasia	0	1 (0.4)	0	0	0	0	1 (1.3)
Headache	0	2 (0.8)	0	1 (5.9)	1 (0.9)	0	0
Hypocalcaemia	0	1 (0.4)	0	0	0	0	1 (1.3)
Ileus	0	1 (0.4)	0	0	1 (0.9)	0	0
Ileus paralytic	0	1 (0.4)	0	0	0	1 (7.1)	0
Leukopenia	0	6 (2.5)	0	0	2 (1.8)	0	4 (5.0)
Lymphocyte count decreased	0	2 (0.8)	0	0	0	1 (7.1)	1 (1.3)
Malaise	0	2 (0.8)	0	0	2 (1.8)	0	0
Neutrophil count decreased	0	11 (4.6)	0	0	6 (5.5)	2 (14.3)	3 (3.8)
Pancytopenia	0	4 (1.7)	1 (5.3)	0	0	0	3 (3.8)
Platelet count decreased	0	5 (2.1)	0	0	3 (2.8)	0	2 (2.5)
Pyrexia	0	1 (0.4)	0	1 (5.9)	0	0	0
Stomatitis	0	1 (0.4)	0	0	0	0	1 (1.3)
Thrombocytopenia	0	4 (1.7)	0	0	2 (1.8)	0	2 (2.5)

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Treatment-emergent adverse events (TEAE) are newly occurring adverse events (not present at baseline) or adverse events that worsen after first dose of study treatment and up through 30 days after the last dose of study treatment.
Related to study treatment as assessed by the investigator.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in tisotumab vedotin column.
For each preferred term, multiple occurrences of events within a subject are counted only once.
Dictionary: MedDRA v26.0
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023
Source: O:\Projects\SGN-TV\SGNTV-003\2023_ia_csr\production\outputs\tlfs\pgms\t-ae-tem-pt.sas Output: t14-05-01-26-ae-pt-tem-rel-ge3-safs.rtf (30OCT23:14:42) Data: adsl, adae

Adverse drug reactions

The events selected for inclusion as ADRs were events with sufficient evidence to establish reasonably likely causal association with tisotumab vedotin, consistent with the SmPC guidelines and Appendix 3 to the Guideline on the clinical evaluation of anticancer medicinal products.

Table 97: Adverse Drug Reactions

System Organ Class	Adverse Reaction	Frequency	Incidence (%)

			Pool 1 (All Cervical) (N=425)	
			Any Grade	Grade 3-4
Nervous system disorders	Peripheral neuropathy[a]	Very common	39	6
Eye disorders	Conjunctival adverse reactions[b]	Very common	36	0.2
	Corneal adverse reactions[c]		20	3
	Dry eye[d]		20	0
	Periorbital adverse reactions[e]		12	0.2
	Eye irritation[f]	Common	7	0
	Symblepharon	Uncommon	0.5	0
Gastrointestinal disorders	Nausea[g]	Very common	37	1
	Constipation		24	1
	Diarrhea[h]		25	2
	Abdominal pain[i]		22	3
	Vomiting		20	2
Respiratory, Thoracic and Mediastinal Disorders	Epistaxis	Very common	33	0
Metabolism and nutrition disorders	Decreased appetite	Very common	23	1
Skin and subcutaneous tissue disorders	Alopecia	Very common	31	0
	Rash[j]		21	1
General disorders and administration site conditions	Pyrexia	Very common	17	1
	Asthenia		14	2
	Fatigue		23	5
	Pruritus		12	0.5

a. Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, muscular weakness, peripheral motor neuropathy, hypoaesthesia, gait disturbance, neuralgia, burning sensation, demyelinating polyneuropathy, neurotoxicity, polyneuropathy, sensory loss, and skin burning sensation.
b. Conjunctival adverse reactions includes conjunctivitis, ocular hyperaemia, conjunctival ulcer, conjunctival hyperaemia, episcleritis, conjunctival scar, conjunctival disorder, conjunctival erosion, conjunctival abrasion, conjunctival oedema, and noninfective conjunctivitis.
c. Corneal adverse reactions includes keratitis, punctate keratitis, ulcerative keratitis, corneal erosion, vital dye staining cornea present, keratopathy, corneal degeneration, corneal irritation, corneal opacity, corneal scar, and corneal thinning.
d. Dry eye includes dry eye and lacrimation increased.
e. Periorbital adverse reactions includes blepharitis, eye pruritus, meibomianitis, trichiasis, entropion, eyelid oedema, madarosis, meibomian gland dysfunction, periorbital oedema, chalazion, erythema of eyelid, eyelid margin crusting, and swelling of eyelid.

f. Eye irritation includes eye discharge, eye pain, eye irritation, and eye oedema.
g. Nausea includes nausea and retching.
h. Diarrhea includes diarrhoea and gastroenteritis.
i. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and abdominal tenderness.
j. Rash includes rash, rash maculo-papular, erythema, eczema, rash macular, dermatitis acneiform, rash pustular, urticaria, dermatitis, dermatitis allergic, rash erythematous, skin irritation, and skin toxicity.

Adverse events of special interest

Adverse events of special interest (AESIs) for tisotumab vedotin include **ocular AEs, peripheral neuropathy, and bleeding AEs.**

Ocular toxicity

Table 98. Summary of Treatment-Emergent Ocular Adverse Events (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any ocular adverse events event	132 (52.8)	15 (6.3)	56 (55.4)	234 (55.1)	353 (56.2)
Grade 1	49 (19.6)	11 (4.6)	24 (23.8)	91 (21.4)	129 (20.5)
Grade 2	73 (29.2)	4 (1.7)	28 (27.7)	127 (29.9)	200 (31.8)
Grade 3	10 (4.0)	0	3 (3.0)	14 (3.3)	21 (3.3)
Grade 4	0	0	1 (1.0)	1 (0.2)	2 (0.3)
Missing	0	0	0	1 (0.2)	1 (0.2)
Subjects with any serious ocular adverse events event	2 (0.8)	0	1 (1.0)	3 (0.7)	5 (0.8)
Subjects with any ocular adverse events event leading to permanent discontinuation	14 (5.6)	0	6 (5.9)	25 (5.9)	37 (5.9)

Ocular adverse events include preferred terms from 9 SMQs and 1 SOC: Conjunctival disorders (narrow), Corneal disorders (broad), Glaucoma (broad), Lacrimal disorders (narrow), Ocular infections (broad), Optic nerve disorders (broad), Periorbital end eyelid disorders (narrow), Retinal disorders (broad), Scleral disorders (narrow), and Eye disorders SOC (primary only).
Multiple occurrences of events within a subject are counted only once.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 99. Treatment-Emergent Ocular Adverse Events in ⩾1% Subjects in SGNTV-003 tisotumab vedotin Arm by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	132 (52.8)	15 (6.3)	56 (55.4)	234 (55.1)	353 (56.2)
Conjunctival disorders	104 (41.6)	7 (2.9)	48 (47.5)	189 (44.5)	293 (46.7)
Conjunctivitis	78 (31.2)	1 (0.4)	31 (30.7)	136 (32.0)	200 (31.8)
Dry eye	33 (13.2)	1 (0.4)	25 (24.8)	73 (17.2)	122 (19.4)
Ocular hyperaemia	4 (1.6)	1 (0.4)	4 (4.0)	8 (1.9)	13 (2.1)
Conjunctival haemorrhage	3 (1.2)	0	2 (2.0)	5 (1.2)	9 (1.4)
Corneal disorders	53 (21.2)	0	21 (20.8)	86 (20.2)	103 (16.4)
Keratitis	39 (15.6)	0	11 (10.9)	53 (12.5)	61 (9.7)
Punctate keratitis	8 (3.2)	0	6 (5.9)	15 (3.5)	20 (3.2)
Lacrimal disorders	6 (2.4)	1 (0.4)	4 (4.0)	11 (2.6)	28 (4.5)
Lacrimation increased	6 (2.4)	1 (0.4)	4 (4.0)	11 (2.6)	28 (4.5)
Non-specific eye disorder	11 (4.4)	2 (0.8)	4 (4.0)	19 (4.5)	32 (5.1)
Eye pain	6 (2.4)	2 (0.8)	1 (1.0)	9 (2.1)	15 (2.4)
Eye irritation	4 (1.6)	0	1 (1.0)	6 (1.4)	10 (1.6)
Other eye disorders	18 (7.2)	2 (0.8)	7 (6.9)	26 (6.1)	33 (5.3)
Eye discharge	11 (4.4)	0	3 (3.0)	14 (3.3)	14 (2.2)
Cataract	5 (2.0)	0	2 (2.0)	8 (1.9)	11 (1.8)
Periorbital and eyelid disorders	23 (9.2)	2 (0.8)	16 (15.8)	47 (11.1)	73 (11.6)
Blepharitis	11 (4.4)	0	7 (6.9)	23 (5.4)	38 (6.1)
Entropion	3 (1.2)	0	3 (3.0)	6 (1.4)	8 (1.3)
Scleral disorders	5 (2.0)	0	0	7 (1.6)	7 (1.1)
Episcleritis	4 (1.6)	0	0	5 (1.2)	5 (0.8)
Vision disorders & symptoms	19 (7.6)	3 (1.3)	7 (6.9)	30 (7.1)	51 (8.1)
Vision blurred	8 (3.2)	2 (0.8)	3 (3.0)	14 (3.3)	29 (4.6)
Eye pruritus	7 (2.8)	0	1 (1.0)	8 (1.9)	14 (2.2)
Photophobia	4 (1.6)	1 (0.4)	1 (1.0)	5 (1.2)	7 (1.1)
Visual acuity reduced	3 (1.2)	0	0	3 (0.7)	3 (0.5)

Ocular adverse events include preferred terms from 9 SMQs and 1 SOC: Conjunctival disorders (narrow), Corneal disorders (broad), Glaucoma (broad), Lacrimal disorders (narrow), Ocular infections (broad), Optic nerve disorders (broad), Periorbital end eyelid disorders (narrow), Retinal disorders (broad), Scleral disorders (narrow), and Eye disorders SOC (primary only).
Multiple occurrences of events within a subject are counted only once.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.

b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 100 Treatment-Emergent ⩾ Grade 3 Ocular Adverse Events by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	10 (4.0)	0	4 (4.0)	15 (3.5)	23 (3.7)
Conjunctival disorders	0	0	0	1 (0.2)	8 (1.3)
Conjunctivitis	0	0	0	1 (0.2)	6 (1.0)
Dry eye	0	0	0	0	2 (0.3)
Corneal disorders	8 (3.2)	0	4 (4.0)	12 (2.8)	14 (2.2)
Keratitis	5 (2.0)	0	0	5 (1.2)	6 (1.0)
Ulcerative keratitis	2 (0.8)	0	4 (4.0)	6 (1.4)	6 (1.0)
Corneal degeneration	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Punctate keratitis	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Corneal lesion	0	0	0	0	1 (0.2)
Other eye disorders	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Cataract	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Periorbital and eyelid disorders	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Entropion	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Meibomian gland dysfunction	0	0	0	0	1 (0.2)

Ocular adverse events include preferred terms from 9 SMQs and 1 SOC: Conjunctival disorders (narrow), Corneal disorders (broad), Glaucoma (broad), Lacrimal disorders (narrow), Ocular infections (broad), Optic nerve disorders (broad), Periorbital end eyelid disorders (narrow), Retinal disorders (broad), Scleral disorders (narrow), and Eye disorders SOC (primary only).
Multiple occurrences of events within a subject are counted only once.
Data are sorted by ascending alphabetical order of classification, and then by descending order of frequency followed by ascending alphabetical order of preferred terms in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 101 Summary of Ocular Treatment-Emergent AE (Safety Analysis Set)

			Chemotherapy				
	Tisotumab Vedotin (N=250)	Chemotherapy (N=239)	Topotecan (N=19)	Vinorelbine (N=17)	Gemcitabine (N=109)	Irinotecan (N=14)	Pemetrexed (N=80)
Subjects with any event, n (%)	132 (52.8)	15 (6.3)	0	0	6 (5.5)	0	9 (11.3)
Grade 1	49 (19.6)	11 (4.6)	0	0	5 (4.6)	0	6 (7.5)
Grade 2	73 (29.2)	4 (1.7)	0	0	1 (0.9)	0	3 (3.8)
Grade 3	10 (4.0)	0	0	0	0	0	0
Subjects with all events resolved[a] or improved[b], n (%)	92/132 (69.7)	11/15 (73.3)	0/0	0/0	5/6 (83.3)	0/0	6/9 (66.7)
Subjects with all events resolved[a]	79/132 (59.8)	11/15 (73.3)	0/0	0/0	5/6 (83.3)	0/0	6/9 (66.7)
Subjects with some events resolved[a] or improved[b], n (%)	32/132 (24.2)	1/15 (6.7)	0/0	0/0	1/6 (16.7)	0/0	0/9
Subjects with no events resolved or improved[b], n (%)	8/132 (6.1)	3/15 (20.0)	0/0	0/0	0/6	0/0	3/9 (33.3)
Subjects with ongoing events at the last follow-up, n (%)	53/132 (40.2)	4/15 (26.7)	0/0	0/0	1/6 (16.7)	0/0	3/9 (33.3)
Grade 1	38/132 (28.8)	3/15 (20.0)	0/0	0/0	1/6 (16.7)	0/0	2/9 (22.2)
Grade 2	9/132 (6.8)	1/15 (6.7)	0/0	0/0	0/6	0/0	1/9 (11.1)
Grade 3	6/132 (4.5)	0/15	0/0	0/0	0/6	0/0	0/9
Time to onset of first event (months)							
n	132	15	0	0	6	0	9
Mean (STD)	1.46 (0.95)	2.66 (2.84)	- (-)	- (-)	1.91 (2.99)	- (-)	3.16 (2.81)
Median	1.22	2.07	-	-	0.30	-	2.56
Min, Max	0.0, 4.9	0.0, 8.3	-, -	-, -	0.0, 7.6	-, -	0.6, 8.3
Number of events	347	18	0	0	9	0	9
Number of events resolved[a]	262	13	0	0	7	0	6
Time to resolution[a] (months)							
n	262	13	0	0	7	0	6
Mean (STD)	1.29 (1.90)	1.00 (1.14)	- (-)	- (-)	1.02 (1.28)	- (-)	0.99 (1.07)
Median	0.59	0.26	-	-	0.26	-	0.61
Min, Max	0.1, 12.6	0.2, 3.7	-, -	-, -	0.2, 3.7	-, -	0.2, 2.9
Number of events with improvement[b]	21	0	0	0	0	0	0
Time to improvement[b] (months)							
n	21	0	0	0	0	0	0
Mean (STD)	0.90 (0.61)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
Median	0.82	-	-	-	-	-	-
Min, Max	0.1, 2.8	-, -	-, -	-, -	-, -	-, -	-, -

Max=maximum; Min=minimum; SMQ=standardized MedDRA query; SOC=system organ class; STD=standard deviation; TEAE=treatment-emergent adverse event.

TEAEs are newly occurring adverse events (not present at baseline) or adverse events that worsen after first dose of study treatment and up through 30 days after the last dose of study treatment.

Ocular adverse events include preferred terms from 9 SMQs and 1 SOC: Conjunctival disorders (narrow), Corneal disorders (broad), Glaucoma (broad), Lacrimal disorders (narrow), Ocular infections (broad), Optic nerve disorders (broad), Periorbital end eyelid disorders (narrow), Retinal disorders (broad), Scleral disorders (narrow), and Eye disorders SOC (primary only).

a. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'. Time to resolution is defined as time (days) from the start date of the event to the end date of the same event (end date of the event - start date of the event + 1).

b. For events that are not resolved, improvement is defined as at least 1 grade decrease from the highest grade as of the last assessment. Time to improvement is time from first occurrence of the highest grade to first improvement (ie, at least 1 grade decrease from the highest grade and no grade increase afterwards).

Updated safety DCO of 16 Jan 2024 for ocular toxicity

Table 102 Summary of Treatment-Emergent Ocular AE tisutumab vedotin Integrated Safety Analysis Set

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1 (All Cervical) (N=425)	Pool 2 (All Tumor Types) (N=628)
Subjects with any event, n (%)	132 (52.8)	15 (6.3)	56 (55.4)	234 (55.1)	353 (56.2)
Subjects with all events resolved [a] or improved [b]	94/132 (71.2%)	11/15 (73.3%)	42/56 (75.0%)	154/234 (65.8%)	209/353 (59.2%)
Subjects with all events resolved [a]	81/132 (61.4%)	11/15 (73.3%)	41/56 (73.2%)	140/234 (59.8%)	193/353 (54.7%)
Subjects with some events resolved [a] or improved [b]	30/132 (22.7%)	1/15 (6.7%)	14/56 (25.0%)	57/234 (24.4%)	95/353 (26.9%)
Subjects with no events resolved [a] or improved [b]	8/132 (6.1%)	3/15 (20.0%)	0/56	23/234 (9.8%)	49/353 (13.9%)
Subjects with ongoing events at the last follow-up					
Maximum Grade 1	36/132 (27.3%)	3/15 (20.0%)	14/56 (25.0%)	64/234 (27.4%)	92/353 (26.1%)
Maximum Grade 2	8/132 (6.1%)	1/15 (6.7%)	1/56 (1.8%)	22/234 (9.4%)	55/353 (15.6%)
Maximum Grade 3	7/132 (5.3%)	0/15	0/56	7/234 (3.0%)	11/353 (3.1%)
Maximum Grade 4	0/132	0/15	0/56	0/234	1/353 (0.3%)
Maximum Grade 5	0/132	0/15	0/56	0/234	0/353
Grade Missing	0/132	0/15	0/56	1/234 (0.4%)	1/353 (0.3%)
Follow-up time after EOT [c] (months)					
n	129	15	56	231	350
Mean (STD)	8.17 (4.59)	6.72 (4.96)	11.59 (9.84)	7.75 (6.94)	6.42 (7.32)
Median	8.11	6.08	8.68	6.77	4.42
Min, Max	0.0, 22.9	0.3, 18.1	0.0, 37.8	0.0, 37.8	0.0, 39.6
Time to onset of first event (months)					
n	132	15	56	234	353
Mean (STD)	1.46 (0.95)	2.66 (2.84)	1.68 (2.32)	1.50 (1.44)	1.32 (1.35)
Median	1.22	2.07	1.41	1.18	0.99
Min, Max	0.0, 4.9	0.0, 8.3	0.0, 17.1	0.0, 17.1	0.0, 17.1
Time to onset of first >= Grade 2 event (months)					
n	83	4	32	142	223
Mean (STD)	2.10 (1.42)	0.65 (0.11)	2.32 (1.22)	2.10 (1.46)	1.84 (1.42)
Median	1.74	0.64	2.12	1.74	1.48
Min, Max	0.1, 6.4	0.6, 0.8	0.4, 5.2	0.1, 9.6	0.0, 9.6
Number of events	351	18	169	627	942
Number of events resolved [a]	269/351 (76.6%)	13/18 (72.2%)	144/169 (85.2%)	481/627 (76.7%)	679/942 (72.1%)
Time to resolution [a] (months)					
n	269	13	144	481	679
Mean (STD)	1.34 (1.92)	1.00 (1.14)	1.35 (1.81)	1.31 (1.81)	1.28 (1.72)
Median	0.59	0.26	0.67	0.62	0.66
Min, Max	0.1, 12.6	0.2, 3.7	0.0, 11.1	0.0, 12.6	0.0, 12.6

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1 (All Cervical) (N=425)	Pool 2 (All Tumor Types) (N=628)
Number of events with improvement [b]	21/351 (6.0%)	0/18	1/169 (0.6%)	22/627 (3.5%)	26/942 (2.8%)
Time to improvement [b] (months)					
n	21	0	1	22	26
Mean (STD)	0.80 (0.62)	- (-)	0.56 (-)	0.79 (0.60)	0.80 (0.61)
Median	0.72	-	0.56	0.67	0.67
Min, Max	0.1, 2.8	-, -	0.6, 0.6	0.1, 2.8	0.1, 2.8

Treatment-emergent adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of study treatment and with onset date on or before 30 days after the last dose of study treatment.
Ocular adverse events include preferred terms from 9 SMQs and 1 SOC: Conjunctival disorders (narrow), Corneal disorders (broad), Glaucoma (broad), Lacrimal disorders (narrow), Ocular infections (broad), Optic nerve disorders (broad), Periorbital and eyelid disorders (narrow), Retinal disorders (broad), Scleral disorders (narrow), and Eye disorders SOC (primary only).
a. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'.
b. For events that are not resolved, improvement is defined as at least one grade decrease from the highest grade as of the last assessment. Time to improvement is time from first occurrence of the highest grade to first improvement (i.e. at least one grade decrease from the highest grade and no grade increase afterwards).
c. EOT date is defined as last dose date + 30 days only when a subject discontinued treatment and did not have end of treatment visit date. EOT date is missing for subjects still receiving ongoing treatment at data cutoff.
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 16Jan2024
Source: O:\Projects\SGN-TV\TV_ISS\2024-06-05-fa-csr-sbla-ema-maa-d120-ir\production\outputs\tlfs\pgms\t-ae-tem-sum-oc.sas Output: t10-05-33-01-ae-tem-sum-oc-safs.rtf (09JUL24:12:50) Data: adsl, adae, adaesi

Peripheral neuropathy

Table 103. Summary of Treatment-Emergent Peripheral Neuropathy (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any treatment-emergent peripheral neuropathy event	96 (38.4)	10 (4.2)	38 (37.6)	165 (38.8)	237 (37.7)
Grade 1	32 (12.8)	5 (2.1)	19 (18.8)	69 (16.2)	99 (15.8)
Grade 2	50 (20.0)	4 (1.7)	12 (11.9)	69 (16.2)	100 (15.9)
Grade 3	14 (5.6)	1 (0.4)	7 (6.9)	27 (6.4)	38 (6.1)
Subjects with any serious peripheral neuropathy event	3 (1.2)	0	3 (3.0)	8 (1.9)	14 (2.2)
Subjects with any peripheral neuropathy event leading to permanent discontinuation	14 (5.6)	0	6 (5.9)	28 (6.6)	45 (7.2)

Peripheral neuropathy adverse events include preferred terms from the Peripheral neuropathy SMQ (broad).
Multiple occurrences of events within a subject are counted only once.
Data are sorted by ascending alphabetical order of classification, and then by descending order of frequency followed by ascending alphabetical order of preferred terms in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 104 TEAEs of Peripheral Neuropathy in ⩾1% Subjects in SGNTV-003 tisotumab vedotin Arm by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy [a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	96 (38.4)	10 (4.2)	38 (37.6)	165 (38.8)	237 (37.7)
Mixed	13 (5.2)	2 (0.8)	11 (10.9)	44 (10.4)	81 (12.9)
Peripheral sensorimotor neuropathy	6 (2.4)	0	6 (5.9)	14 (3.3)	16 (2.5)
Neurotoxicity	4 (1.6)	0	0	4 (0.9)	4 (0.6)
Gait disturbance	3 (1.2)	1 (0.4)	1 (1.0)	5 (1.2)	7 (1.1)
Motor	12 (4.8)	0	5 (5.0)	22 (5.2)	38 (6.1)
Muscular weakness	7 (2.8)	0	2 (2.0)	12 (2.8)	24 (3.8)
Peripheral motor neuropathy	5 (2.0)	0	3 (3.0)	10 (2.4)	15 (2.4)
Sensory	84 (33.6)	8 (3.3)	28 (27.7)	124 (29.2)	159 (25.3)
Peripheral sensory neuropathy	71 (28.4)	6 (2.5)	19 (18.8)	99 (23.3)	130 (20.7)
Paraesthesia	10 (4.0)	1 (0.4)	4 (4.0)	16 (3.8)	19 (3.0)
Neuralgia	3 (1.2)	1 (0.4)	2 (2.0)	5 (1.2)	5 (0.8)

Peripheral neuropathy adverse events include preferred terms from the Peripheral neuropathy SMQ (broad).
Multiple occurrences of events within a subject are counted only once.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 105 Treatment-Emergent ⩾ Grade 3 Adverse Events of Peripheral Neuropathy by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	14 (5.6)	1 (0.4)	7 (6.9)	27 (6.4)	38 (6.1)
Mixed	4 (1.6)	0	3 (3.0)	11 (2.6)	14 (2.2)
Gait disturbance	3 (1.2)	0	0	3 (0.7)	3 (0.5)
Peripheral sensorimotor neuropathy	2 (0.8)	0	2 (2.0)	6 (1.4)	6 (1.0)
Demyelinating polyneuropathy	0	0	0	1 (0.2)	1 (0.2)
Neuropathy peripheral	0	0	1 (1.0)	2 (0.5)	3 (0.5)
Polyneuropathy	0	0	0	0	2 (0.3)
Motor	2 (0.8)	0	2 (2.0)	5 (1.2)	8 (1.3)

Classification Preferred Term	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250) n (%)	 Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Muscular weakness	2 (0.8)	0	0	2 (0.5)	5 (0.8)
Peripheral motor neuropathy	0	0	2 (2.0)	3 (0.7)	4 (0.6)
Sensory	9 (3.6)	1 (0.4)	2 (2.0)	12 (2.8)	17 (2.7)
Peripheral sensory neuropathy	7 (2.8)	0	2 (2.0)	10 (2.4)	15 (2.4)
Neuralgia	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Paraesthesia	1 (0.4)	0	0	1 (0.2)	1 (0.2)

Peripheral neuropathy adverse events include preferred terms from the Peripheral neuropathy SMQ (broad).
Multiple occurrences of events within a subject are counted only once.
Data are sorted by ascending alphabetical order of classification, and then by descending order of frequency followed by ascending alphabetical order of preferred terms in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 106 Onset and Resolution of Treatment-Emergent Peripheral Neuropathy (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250)	 Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumour Types) (N=628)
Subjects with any event, n (%)	96 (38.4)	10 (4.2)	38 (37.6)	165 (38.8)	237 (37.7)
Time to onset of first event (months)					
n	96	10	38	165	237
Mean (STD)	2.66 (1.94)	1.91 (1.97)	3.08 (2.30)	2.80 (2.10)	2.57 (1.97)
Median	2.38	1.15	2.46	2.43	2.20
Min, Max	0.0, 9.3	0.1, 5.6	0.0, 11.3	0.0, 11.3	0.0, 11.3
Subjects with all events resolved[d] or improved [b]	35/96 (36.5%)	5/10 (50.0%)	10/38 (26.3%)	49/165 (29.7%)	63/237 (26.6%)
Subjects with some events resolved[d] or improved[e]	7/96 (7.3%)	1/10 (10.0%)	6/38 (15.8%)	15/165 (9.1%)	24/237 (10.1%)
Subjects with no events resolved[d] or improved[e]	54/96 (56.3%)	4/10 (40.0%)	22/38 (57.9%)	101/165 (61.2%)	150/237 (63.3%)
Number of events	123	11	58	225	326
Number of events resolved[d]	31/123 (25.2%)	5/11 (45.5%)	14/58 (24.1%)	53/225 (23.6%)	74/326 (22.7%)
Time to resolution[d] (months)					
n	31	5	14	53	74
Mean (STD)	1.85 (2.74)	2.39 (2.54)	2.33 (5.45)	1.83 (3.49)	1.71 (3.29)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumour Types) (N=628)
Median	1.12	1.31	0.54	0.72	0.66
Min, Max	0.0, 12.1	0.2, 5.4	0.0, 20.7	0.0, 20.7	0.0, 20.7
Subjects with ongoing events at the last follow-up					
Maximum Grade 1	42/96 (43.8%)	5/10 (50.0%)	17/38 (44.7%)	74/165 (44.8%)	104/237 (43.9%)
Maximum Grade 2	30/96 (31.3%)	0/10	9/38 (23.7%)	45/165 (27.3%)	70/237 (29.5%)
Maximum Grade 3	6/96 (6.3%)	1/10 (10.0%)	5/38 (13.2%)	17/165 (10.3%)	26/237 (11.0%)
Follow-up time after EOT[f] (months)					
n	84	9	38	153	225
Mean (STD)	5.77 (4.36)	5.04 (3.15)	12.35 (10.09)	6.57 (7.10)	5.50 (6.97)
Median	4.40	5.55	8.81	4.40	3.12
Min, Max	0.0, 17.7	0.0, 10.1	0.0, 37.5	0.0, 37.5	0.0, 37.5

Peripheral neuropathy adverse events include preferred terms from the Peripheral neuropathy SMQ (broad).
STD= standard deviation.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'.
e. For events that are not resolved, improvement is defined as at least one grade decrease from the highest grade as of the last assessment. Time to improvement is time from first occurrence of the highest grade to first improvement (i.e., at least one grade decrease from the highest grade and no grade increase afterwards).
f. EOT date is defined as last dose date + 30 days only when a subject discontinued treatment and did not have end of treatment visit date. EOT date is missing for subjects still receiving ongoing treatment at data cutoff.
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

As of the updated DCO of 16 Jan 2024, 96 (38.4%) patients experienced peripheral neuropathy in the TV arm in SGNTV-003. Of these, 81 (61.4%) patients had all events resolved; while another 30 (22.7%) patients experienced either complete resolution or partial improvement. The median time to resolution was 1.12 months and median time to improvement was 1.41 months. 10.4% had a dose reduction; while 6% had peripheral neuropathy leading to permanent treatment discontinuation of which 40% of the patients had resolution or improvement.

Bleeding Adverse events

Table 107. Summary of Treatment-Emergent Bleeding Adverse Events (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any bleeding event	105 (42.0)	34 (14.2)	57 (56.4)	216 (50.8)	342 (54.5)
Grade 1	80 (32.0)	14 (5.9)	45 (44.6)	169 (39.8)	277 (44.1)
Grade 2	19 (7.6)	13 (5.4)	5 (5.0)	29 (6.8)	39 (6.2)
Grade 3	5 (2.0)	6 (2.5)	7 (6.9)	17 (4.0)	25 (4.0)
Grade 4	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Subjects with any serious bleeding event	6 (2.4)	9 (3.8)	5 (5.0)	16 (3.8)	26 (4.1)
Subjects with any bleeding event leading to permanent discontinuation	0	0	0	1 (0.2)	4 (0.6)

Bleeding adverse events include preferred terms from 2 SMQs: Haemorrhage terms (excl laboratory terms) (narrow) and Haemorrhage laboratory terms (narrow).
Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 108. Treatment-Emergent Bleeding Adverse Events in ⩾1% Subjects in SGNTV-003 tisotumab vedotin Arm by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	105 (42.0)	34 (14.2)	57 (56.4)	216 (50.8)	342 (54.5)
Epistaxis	65 (26.0)	6 (2.5)	39 (38.6)	142 (33.4)	252 (40.1)
Vaginal haemorrhage	25 (10.0)	13 (5.4)	12 (11.9)	43 (10.1)	46 (7.3)
Haematuria	18 (7.2)	5 (2.1)	10 (9.9)	35 (8.2)	43 (6.8)
Rectal haemorrhage	5 (2.0)	5 (2.1)	4 (4.0)	11 (2.6)	15 (2.4)
Conjunctival haemorrhage	3 (1.2)	0	2 (2.0)	5 (1.2)	9 (1.4)
Haematochezia	3 (1.2)	3 (1.3)	2 (2.0)	8 (1.9)	9 (1.4)
Uterine haemorrhage	3 (1.2)	0	0	3 (0.7)	3 (0.5)

Bleeding adverse events include preferred terms from 2 SMQs: Haemorrhage terms (excl laboratory terms) (narrow) and Haemorrhage laboratory terms (narrow).
Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 109 Treatment-Emergent ⩾ Grade 3 Bleeding Adverse Events by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	6 (2.4)	7 (2.9)	7 (6.9)	18 (4.2)	26 (4.1)
Vaginal haemorrhage	3 (1.2)	1 (0.4)	2 (2.0)	6 (1.4)	6 (1.0)
Disseminated intravascular coagulation	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Haematochezia	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Haematuria	1 (0.4)	1 (0.4)	2 (2.0)	4 (0.9)	6 (1.0)
Haemorrhage	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Cystitis haemorrhagic	0	0	1 (1.0)	1 (0.2)	1 (0.2)
Gastric ulcer haemorrhage	0	0	0	0	1 (0.2)
Gastrointestinal haemorrhage	0	2 (0.8)	0	0	1 (0.2)
Gastrointestinal ulcer haemorrhage	0	0	0	0	1 (0.2)
Intermenstrual bleeding	0	2 (0.8)	0	0	0
Lower gastrointestinal haemorrhage	0	0	0	1 (0.2)	1 (0.2)
Post procedural haemorrhage	0	0	0	0	1 (0.2)
Rectal haemorrhage	0	2 (0.8)	2 (2.0)	2 (0.5)	2 (0.3)
Shock haemorrhagic	0	1 (0.4)	0	0	0
Tumour haemorrhage	0	0	0	2 (0.5)	2 (0.3)
Upper gastrointestinal haemorrhage	0	0	0	0	1 (0.2)

Bleeding adverse events include preferred terms from 2 SMQs: Haemorrhage terms (excl laboratory terms) (narrow) and Haemorrhage laboratory terms (narrow).
Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 110 Onset and Resolution of Treatment-Emergent Bleeding Adverse Events (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumour Types) (N=628)
Subjects with any event, n (%)	105 (42.0)	34 (14.2)	57 (56.4)	216 (50.8)	342 (54.5)
Time to onset of first event (months)					
n	105	34	57	216	342
Mean (STD)	1.30 (1.99)	1.48 (1.49)	0.90 (1.36)	1.01 (1.62)	0.83 (1.38)
Median	0.43	0.92	0.30	0.31	0.28
Min, Max	0.0, 10.4	0.0, 4.8	0.0, 6.5	0.0, 10.4	0.0, 10.4
Subjects with all events resolved[d] or improved[e]	77/105 (73.3%)	19/34 (55.9%)	45/57 (78.9%)	156/216 (72.2%)	236/342 (69.0%)
Subjects with some events resolved[d] or improved[e]	11/105 (10.5%)	2/34 (5.9%)	6/57 (10.5%)	23/216 (10.6%)	40/342 (11.7%)
Subjects with no events resolved[d] or improved[e]	17/105 (16.2%)	13/34 (38.2%)	6/57 (10.5%)	37/216 (17.1%)	66/342 (19.3%)
Number of events	168	47	101	375	574
Number of events resolved[d]	135/168 (80.4%)	27/47 (57.4%)	87/101 (86.1%)	302/375 (80.5%)	453/574 (78.9%)
Time to resolution[d] (months)					
n	135	27	87	302	453
Mean (STD)	0.84 (1.42)	0.57 (0.82)	1.04 (1.50)	0.86 (1.39)	0.84 (1.31)
Median	0.26	0.16	0.33	0.28	0.30
Min, Max	0.0, 7.2	0.0, 2.9	0.0, 6.1	0.0, 7.2	0.0, 7.4
Subjects with ongoing events at the last follow-up					
Maximum Grade 1	23/105 (21.9%)	8/34 (23.5%)	9/57 (15.8%)	48/216 (22.2%)	91/342 (26.6%)
Maximum Grade 2	5/105 (4.8%)	5/34 (14.7%)	2/57 (3.5%)	10/216 (4.6%)	12/342 (3.5%)
Maximum Grade 3	0/105	1/34 (2.9%)	2/57 (3.5%)	4/216 (1.9%)	4/342 (1.2%)
Maximum Grade 4	1/105 (1.0%)	1/34 (2.9%)	0/57	1/216 (0.5%)	1/342 (0.3%)

Bleeding adverse events include preferred terms from 2 SMQs: Haemorrhage terms (excl laboratory terms) (narrow) and Haemorrhage laboratory terms (narrow).
STD= standard deviation.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'.
e. For events that are not resolved, improvement is defined as at least one grade decrease from the highest grade as of the last assessment. Time to improvement is time from first occurrence of the highest grade to first improvement (i.e., at least one grade decrease from the highest grade and no grade increase afterwards).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 111 Treatment-Emergent Bleeding Adverse Events by PT and Maximum Severity and Baseline Hepatic Function (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin		SGNTV-003 (Pivotal Cervical) Chemotherapy		GCT1015-04 (Supportive Cervical)		Pool 1 (All Cervical)		Pool 2 (All Tumor Types)	
Preferred Term Severity	Normal (N=220) n (%)	Mild (N=30) n (%)	Normal (N=205) n (%)	Mild (N=34) n (%)	Normal (N=93) n (%)	Mild (N=8) n (%)	Normal (N=376) n (%)	Mild (N=49) n (%)	Normal (N=549) n (%)	Mild (N=79) n (%)
Subjects with any event	94 (42.7)	11 (36.7)	31 (15.1)	3 (8.8)	55 (59.1)	2 (25.0)	196 (52.1)	20 (40.8)	304 (55.4)	38 (48.1)
Grade 1	71 (32.3)	9 (30.0)	12 (5.9)	2 (5.9)	44 (47.3)	1 (12.5)	154 (41.0)	15 (30.6)	248 (45.2)	29 (36.7)
Grade 2	18 (8.2)	1 (3.3)	12 (5.9)	1 (2.9)	4 (4.3)	1 (12.5)	27 (7.2)	2 (4.1)	36 (6.6)	3 (3.8)
Grade 3	4 (1.8)	1 (3.3)	6 (2.9)	0	7 (7.5)	0	14 (3.7)	3 (6.1)	19 (3.5)	6 (7.6)
Grade 4	1 (0.5)	0	1 (0.5)	0	0	0	1 (0.3)	0	1 (0.2)	0
Epistaxis	57 (25.9)	8 (26.7)	5 (2.4)	1 (2.9)	38 (40.9)	1 (12.5)	127 (33.8)	15 (30.6)	223 (40.6)	29 (36.7)
Grade 1	54 (24.5)	8 (26.7)	5 (2.4)	1 (2.9)	36 (38.7)	0	121 (32.2)	14 (28.6)	216 (39.3)	28 (35.4)
Grade 2	3 (1.4)	0	0	0	2 (2.2)	1 (12.5)	6 (1.6)	1 (2.0)	7 (1.3)	1 (1.3)
Vaginal haemorrhage	23 (10.5)	2 (6.7)	12 (5.9)	1 (2.9)	12 (12.9)	0	40 (10.6)	3 (6.1)	43 (7.8)	3 (3.8)
Grade 1	17 (7.7)	1 (3.3)	5 (2.4)	1 (2.9)	10 (10.8)	0	30 (8.0)	2 (4.1)	33 (6.0)	2 (2.5)
Grade 2	3 (1.4)	1 (3.3)	6 (2.9)	0	0	0	4 (1.1)	1 (2.0)	4 (0.7)	1 (1.3)
Grade 3	3 (1.4)	0	0	0	2 (2.2)	0	6 (1.6)	0	6 (1.1)	0
Grade 4	0	0	1 (0.5)	0	0	0	0	0	0	0
Haematuria	16 (7.3)	2 (6.7)	4 (2.0)	1 (2.9)	10 (10.8)	0	33 (8.8)	2 (4.1)	39 (7.1)	4 (5.1)
Grade 1	10 (4.5)	2 (6.7)	2 (1.0)	1 (2.9)	7 (7.5)	0	23 (6.1)	2 (4.1)	26 (4.7)	4 (5.1)
Grade 2	5 (2.3)	0	1 (0.5)	0	1 (1.1)	0	6 (1.6)	0	7 (1.3)	0
Grade 3	1 (0.5)	0	1 (0.5)	0	2 (2.2)	0	4 (1.1)	0	6 (1.1)	0

Treatment-emergent adverse events (TEAE), defined as newly occurring adverse events (not present at baseline) or adverse events that worsen after first dose of study treatment and up through 30 days after the last dose of study treatment, are presented.
Bleeding adverse events include preferred terms from 2 SMQs: Haemorrhage terms (excl laboratory terms) (narrow) and Haemorrhage laboratory terms (narrow).
At each preferred term, multiple occurrences of events within a subject are counted only once at the highest severity grade.
Dictionary: MedDRA v26.0, Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023
Source: O:\Projects\SGN-TV\TV_ISS\2024-04-29-sbla-ema-maa-d80-ir\production\outputs\tlfs\pgms\t-ae-tem-pt-grd-bl-hepa.sas Output: t10-05-35-17-ae-tem-pt-grd-bl-hepa-safs.rtf (17JUN24:17:07) Data: adsl, adae

Epistaxis was the most common bleeding event (26.0% in the TV arm vs 2.5% in the chemotherapy arm). All events of epistaxis in the TV arm were non-serious and mostly grade 1 (24.8%), which is self-limited and did not require intervention. No Grade 3 or higher epistaxis were reported and most events had improved or resolved in approximately 2 weeks (81.5%).

The high-grade bleeding events observed were mainly bleeding at the location of the tumour,

Infusion-Related Reactions

In the TV arm of SGNTV-003, 16 (6.4%) subjects experienced an IRR TEAE compared to 1.3% of subjects in the chemotherapy arm. All IRR TEAEs in the TV were grade 1 (3.2%) or grade 2 (3.2%). None of the events met Sampson's criteria (Sampson 2006). Only 1 subject experienced an IRR SAE.

Of the 16 IRR cases in the SGNTV-003 tisotumab vedotin arm, 7 subjects recovered without treatment and 7 subjects recovered after treatment with acetaminophen, antiemetics, antihistamines, hydration, and/or corticosteroids. Two subjects had ongoing IRR events from Cycle 1 through last follow-up (grade 2 rash pustular and Grade 1 nausea) although both subjects received subsequent dose(s) of tisotumab vedotin without worsening of their events.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reaction (SCAR) was evaluated in the SGNTV-003 study. Two subjects (0.8%) experienced SJS in tisotumab vedotin arm and 1 subject (0.4%) experienced SJS in the chemotherapy arm.

Severe cutaneous adverse reaction (SCAR) TEAEs are summarised in Table 116. The most common events in the TV arm were erythema multiforme and SJS. Summaries of the 2 patients with ≥ Grade 3 and serious events of SCAR, which were both SJS were provided.

In the GCT1015-04 study, no subjects experienced SCARs events.

Table 112 Summary of TEAEs of Severe Cutaneous Adverse Reactions (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification	**Tisotumab Vedotin (N=250)**	**Chemotherapy[a] (N=239)**	**GCT1015-04 (Supportive Cervical) (N=101)**	**Pool 1[b] (All Cervical) (N=425)**	**Pool 2[c] (All Tumour Types) (N=628)**
Subjects with any SCAR event, n (%)	6 (2.4)	3 (1.3)	0	7 (1.6)	9 (1.4)
Grade 1	2 (0.8)	1 (0.4)	0	3 (0.7)	4 (0.6)
Grade 2	2 (0.8)	0	0	2 (0.5)	3 (0.5)
Grade 3	1 (0.4)	2 (0.8)	0	1 (0.2)	1 (0.2)
Grade 5	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Subjects with any serious SCAR event, n (%)	2 (0.8)	2 (0.8)	0	2 (0.5)	2 (0.3)
Subjects with any SCAR event leading to discontinuation, n (%)	2 (0.8)	1 (0.4)	0	2 (0.5)	2 (0.3)
Time to onset of first event (months)					
n	6	3	0	7	9
Mean (STD)	0.41 (0.34)	1.03 (0.71)	- (-)	0.36 (0.33)	0.45 (0.46)
Median	0.23	1.02	-	0.20	0.20
Min, Max	0.1, 0.9	0.3, 1.7	-, -	0.1, 0.9	0.1, 1.4
Subjects with all events resolved[d] or improved[e]	3/6 (50.0%)	2/3 (66.7%)	0/0	3/7 (42.9%)	5/9 (55.6%)
Subjects with some events resolved[d] or improved[e]	0/6	1/3 (33.3%)	0/0	0/7	0/9
Subjects with no events resolved[d] or improved[e]	3/6 (50.0%)	0/3	0/0	4/7 (57.1%)	4/9 (44.4%)
Number of events	7	4	0	8	10
Number of events resolved[d]	4/7 (57.1%)	3/4 (75.0%)	0/0	4/8 (50.0%)	6/10 (60.0%)
Time to resolution[d] (months)					
n	4	3	0	4	6
Mean (STD)	1.08 (0.83)	0.92 (0.46)	- (-)	1.08 (0.83)	0.78 (0.80)
Median	0.79	1.12	-	0.79	0.51
Min, Max	0.5, 2.3	0.4, 1.2	-, -	0.5, 2.3	0.0, 2.3
Subjects with ongoing events at the last follow-up					
Maximum Grade 1	0/6	1/3 (33.3%)	0/0	1/7 (14.3%)	1/9 (11.1%)
Maximum Grade 2	1/6 (16.7%)	0/3	0/0	1/7 (14.3%)	1/9 (11.1%)
Maximum Grade 3	1/6 (16.7%)	0/3	0/0	1/7 (14.3%)	1/9 (11.1%)
Maximum Grade 4	0/6	0/3	0/0	0/7	0/9
Maximum Grade 5	1/6 (16.7%)	0/3	0/0	1/7 (14.3%)	1/9 (11.1%)

Severe cutaneous adverse reactions include preferred terms from the Severe cutaneous adverse reactions SMQ (narrow).
SCAR=severe cutaneous adverse reaction; STD= standard deviation.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'.

e. For events that are not resolved, improvement is defined as at least one grade decrease from the highest grade as of the last assessment. Time to improvement is time from first occurrence of the highest grade to first improvement (i.e., at least one grade decrease from the highest grade and no grade increase afterwards).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 113:TEAEs of Severe Cutaneous Adverse Reactions by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Preferred Term	**Tisotumab Vedotin (N=250) n (%)**	**Chemotherapy[a] (N=239) n (%)**	**GCT1015-04 (Supportive Cervical) (N=101) n (%)**	**Pool 1[b] (All Cervical) (N=425) n (%)**	**Pool 2[c] (All Tumour Types) (N=628) n (%)**
Subjects with any event	6 (2.4)	3 (1.3)	0	7 (1.6)	9 (1.4)
Erythema multiforme	3 (1.2)	1 (0.4)	0	3 (0.7)	3 (0.5)
Stevens-Johnson syndrome	2 (0.8)	1 (0.4)	0	2 (0.5)	2 (0.3)
Dermatitis bullous	1 (0.4)	0	0	2 (0.5)	3 (0.5)
Drug reaction with eosinophilia and systemic symptoms	0	1 (0.4)	0	0	0
Toxic skin eruption	0	0	0	0	1 (0.2)

Severe cutaneous adverse reactions include preferred terms from the Severe cutaneous adverse reactions SMQ (narrow).
Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

2.4.8.2. Serious adverse event/deaths/other significant events

Table 114 Treatment-Emergent SAEs Reported in ⩾1% of Subjects in the SGNTV-003 tisotumab vedotin or Chemotherapy Arm by PT (Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event[d]	82 (32.8)	94 (39.3)	44 (43.6)	159 (37.4)	243 (38.7)
Urinary tract infection	10 (4.0)	17 (7.1)	3 (3.0)	15 (3.5)	19 (3.0)
Small intestinal obstruction	6 (2.4)	1 (0.4)	0	6 (1.4)	10 (1.6)
Abdominal pain	5 (2.0)	2 (0.8)	1 (1.0)	8 (1.9)	13 (2.1)
Sepsis	5 (2.0)	2 (0.8)	0	5 (1.2)	9 (1.4)
Pyrexia	4 (1.6)	4 (1.7)	3 (3.0)	9 (2.1)	10 (1.6)
Vaginal haemorrhage	4 (1.6)	3 (1.3)	2 (2.0)	7 (1.6)	7 (1.1)
Vomiting	4 (1.6)	2 (0.8)	1 (1.0)	9 (2.1)	12 (1.9)
Acute kidney injury	3 (1.2)	5 (2.1)	1 (1.0)	4 (0.9)	5 (0.8)
Constipation	3 (1.2)	0	3 (3.0)	8 (1.9)	13 (2.1)
Fatigue	3 (1.2)	4 (1.7)	0	4 (0.9)	5 (0.8)
Hyponatraemia	3 (1.2)	0	0	3 (0.7)	7 (1.1)
Pelvic pain	3 (1.2)	0	0	3 (0.7)	3 (0.5)
Anaemia	2 (0.8)	10 (4.2)	2 (2.0)	5 (1.2)	7 (1.1)
Hydronephrosis	2 (0.8)	7 (2.9)	0	2 (0.5)	2 (0.3)
Neutropenia	2 (0.8)	4 (1.7)	0	2 (0.5)	3 (0.5)
Pneumonia	2 (0.8)	3 (1.3)	4 (4.0)	6 (1.4)	11 (1.8)
Febrile neutropenia	1 (0.4)	8 (3.3)	0	2 (0.5)	5 (0.8)
Pyelonephritis	1 (0.4)	3 (1.3)	0	2 (0.5)	3 (0.5)
COVID-19	0	3 (1.3)	0	0	0
Nausea	0	3 (1.3)	0	3 (0.7)	4 (0.6)
Pancytopenia	0	4 (1.7)	0	0	0

Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 115 Treatment-Related Treatment-Emergent SAEs in ⩾1% of Subjects in the SGNTV-003 tisotumab vedotin or Chemotherapy Arm by PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	26 (10.4)	35 (14.6)	14 (13.9)	57 (13.4)	94 (15.0)
Fatigue	3 (1.2)	2 (0.8)	0	4 (0.9)	5 (0.8)
Vomiting	3 (1.2)	0	0	6 (1.4)	6 (1.0)
Neutropenia	2 (0.8)	3 (1.3)	0	2 (0.5)	3 (0.5)
Anaemia	1 (0.4)	7 (2.9)	1 (1.0)	3 (0.7)	4 (0.6)
Febrile neutropenia	1 (0.4)	7 (2.9)	0	2 (0.5)	5 (0.8)
Urinary tract infection	1 (0.4)	3 (1.3)	0	1 (0.2)	1 (0.2)
Pancytopenia	0	4 (1.7)	0	0	0

Related to study treatment as assessed by the investigator.
Multiple occurrences of events within a subject are counted only once.
Data are sorted by descending order of frequency.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 116 Summary of Deaths Within 30 Days of Last Study Treatment (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumour Types) (N=628)
Deaths within 30 days from last dose date	12 (4.8)	18 (7.5)	9 (8.9)	23 (5.4)	32 (5.1)
Disease related[d]	8 (3.2)	11 (4.6)	6 (5.9)	15 (3.5)	24 (3.8)
Adverse event	4 (1.6)	5 (2.1)	2 (2.0)	7 (1.6)	7 (1.1)
Acute kidney injury	1 (0.4)	0	0	1 (0.2)	1 (0.2)
COVID-19	0	1 (0.4)	0	0	0
Pancytopenia	0	1 (0.4)	0	0	0
Pneumonia	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Respiratory failure	0	1 (0.4)	0	0	0
Sepsis	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Septic shock	0	1 (0.4)	1 (1.0)	1 (0.2)	1 (0.2)
Stevens-Johnson syndrome	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Unknown cause of death	0	0	1 (1.0)	1 (0.2)	1 (0.2)
Worsening of cervical cancer	0	0	0	1 (0.2)	1 (0.2)
Not available / Unknown[e]	0	2 (0.8)	1 (1.0)	1 (0.2)	1 (0.2)

Survival status was not followed up in GEN701, GEN702, GCT1015-03.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. Includes investigator assessed disease related deaths, deaths due to deterioration of underlying cancer disease, and deaths due to disease progression.
e. Cause of death may not be available in SGNTV-003 when death date was gathered from public registry or medical record, per subject's wishes and local regulations.
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

2.4.8.3. Laboratory findings

Table 117 Treatment-Emergent Laboratory Abnormalities SGNTV-003 (Safety Analysis Set)

	Tisotumab Vedotin (N=250)				Chemotherapy[b] (N=239)			
Parameter	n[a]	Grade 1+2 n (%)	Grade 3 n (%)	Grade 4 n (%)	n[a]	Grade 1+2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematology								
Hemoglobin decreased	244	83 (34.0)	17 (7.0)	0	230	108 (47.0)	53 (23.0)	0
Hemoglobin increased	244	3 (1.2)	0	0	230	1 (0.4)	0	0
Leukocytes decreased	244	59 (24.2)	1 (0.4)	0	230	71 (30.9)	20 (8.7)	5 (2.2)
Lymphocytes decreased	224	59 (26.3)	15 (6.7)	0	218	69 (31.7)	32 (14.7)	2 (0.9)
Lymphocytes increased	224	1 (0.4)	0	0	218	1 (0.5)	0	0
Neutrophils decreased	244	32 (13.1)	8 (3.3)	0	229	51 (22.3)	29 (12.7)	10 (4.4)
Platelets decreased	244	11 (4.5)	0	0	230	53 (23.0)	3 (1.3)	5 (2.2)
Chemistry								
Alanine Aminotransferase increased	243	65 (26.7)	6 (2.5)	2 (0.8)	230	75 (32.6)	6 (2.6)	0
Albumin decreased	244	51 (20.9)	3 (1.2)	0	230	75 (32.6)	6 (2.6)	0
Alkaline Phosphatase increased	243	53 (21.8)	0	0	229	62 (27.1)	0	0
Aspartate Aminotransferase increased	242	76 (31.4)	5 (2.1)	1 (0.4)	228	71 (31.1)	1 (0.4)	0
Calcium Corrected for Albumin decreased	242	15 (6.2)	1 (0.4)	0	229	19 (8.3)	0	0
Calcium Corrected for Albumin increased	242	42 (17.4)	1 (0.4)	3 (1.2)	229	27 (11.8)	2 (0.9)	0
Creatinine increased	244	51 (20.9)	5 (2.0)	0	229	55 (24.0)	5 (2.2)	0
Glomerular Filtration Rate, Estimated decreased	117	23 (19.7)	3 (2.6)	1 (0.9)	107	22 (20.6)	4 (3.7)	1 (0.9)
Glucose decreased	242	15 (6.2)	0	0	226	9 (4.0)	0	0
Lactate Dehydrogenase increased	238	89 (37.4)	0	0	226	83 (36.7)	0	0
Magnesium decreased	243	47 (19.3)	0	1 (0.4)	228	45 (19.7)	1 (0.4)	0
Magnesium increased	243	4 (1.6)	0	0	228	3 (1.3)	0	0
Potassium decreased	244	38 (15.6)	6 (2.5)	0	230	33 (14.3)	7 (3.0)	0
Potassium increased	244	24 (9.8)	0	0	230	30 (13.0)	0	0
Sodium decreased	244	65 (26.6)	1 (0.4)	0	230	61 (26.5)	0	1 (0.4)
Sodium increased	244	4 (1.6)	0	0	230	7 (3.0)	0	0
Total Bilirubin increased	243	4 (1.6)	1 (0.4)	0	230	4 (1.7)	0	0

Coagulation								
Activated Partial Thromboplastin Time increased	211	30 (14.2)	4 (1.9)	0	206	34 (16.5)	1 (0.5)	0
Fibrinogen decreased	232	5 (2.2)	1 (0.4)	0	208	1 (0.5)	0	0
Prothrombin Intl. Normalized Ratio increased	241	22 (9.1)	0	0	223	23 (10.3)	1 (0.4)	0

a. The denominators for the percentage are the number of subjects in the Safety Analysis Set with both baseline and post-baseline results for each test.
b. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
Baseline is defined as the last non-missing lab results before the first dose. Post-baseline is defined as the lab results after the first dose and through 30 days after last dose or the EOT visit, whichever is later. Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any post-baseline time point. Includes treatment-emergent laboratory abnormalities, reported during the study, that were new or worsening in grade or any abnormality when baseline grade was unknown.
If baseline grade and post-baseline grade were in different directions for a bi-directional lab test (e.g., from baseline high to post-baseline low), it is considered treatment-emergent. A subject is summarized at the maximum grade for the applicable direction (e.g., increased or decreased) in the lab test.
Grades were derived based on numeric criteria as defined in CTCAE v5.0 and did not take into consideration clinical signs or symptoms which are needed for the final grade associated with the adverse event.
Snapshot Date: 21AUG2023, Data Cutoff Date: 24JUL2023

ECG findings:

For all patients, one 12-lead electrocardiogram (ECG) was performed at screening, at the end of treatment visit, and as clinically indicated during the treatment period. ECGs were locally evaluated by investigator. No quantative ECG data was collected, as concentration-ΔQTcF analysis did not show clinically relevant ΔQTcF risk at Cmax of both ADC and MMAE with TV 2.0 mg/kg Q3W.

Summary of findings (refer to listing 16.2.11.8):

- 3 patients experienced clinically significant ECG abnormalities at baseline (N=1 in TV vs. N=2 in chemotherapy arm, respectively)
- 1 patient in the chemotherapy arm had clinically significant ECG abnormalities post-baseline recorded as TEAE (sinus bradycardia [Grade 1], assessed as not related)
- 22 patients in TV arm and 18 patients in chemotheraphy arm, with normal baseline ECG, experienced not clinically relevant ECG changes at the end of treatment

2.4.8.4. Safety in special populations

Table 118 Adverse Events by Age Range SGNTV-003 (Safety Analysis Set)

	Tisotumab Vedotin (N=250)				Chemotherapy[a] (N=239)			
	Age <65 (N=209) n (%)	Age 65-74 (N=33) n (%)	Age 75-84 (N=8) n (%)	Age >=85 (N=0) n (%)	Age <65 (N=201) n (%)	Age 65-74 (N=33) n (%)	Age 75-84 (N=5) n (%)	Age >=85 (N=0) n (%)
Total AEs	205 (98.1)	33 (100)	8 (100)	0	199 (99.0)	33 (100)	5 (100)	0
Serious AEs	69 (33.0)	11 (33.3)	2 (25.0)	0	77 (38.3)	15 (45.5)	2 (40.0)	0
Fatal	3 (1.4)	1 (3.0)	0	0	4 (2.0)	1 (3.0)	0	0
Hospitalization/prolong existing hospitalization	65 (31.1)	10 (30.3)	2 (25.0)	0	74 (36.8)	15 (45.5)	2 (40.0)	0
Life threatening	5 (2.4)	1 (3.0)	0	0	6 (3.0)	1 (3.0)	0	0
Disability/incapacity	2 (1.0)	0	0	0	0	0	0	0
Other (medically significant)	6 (2.9)	1 (3.0)	0	0	3 (1.5)	1 (3.0)	0	0
AE leading to drop-out[b]	27 (12.9)	8 (24.2)	2 (25.0)	0	9 (4.5)	0	0	0
Psychiatric disorders[c]	22 (10.5)	3 (9.1)	2 (25.0)	0	21 (10.4)	2 (6.1)	0	0
Nervous system disorders[c]	89 (42.6)	10 (30.3)	5 (62.5)	0	32 (15.9)	8 (24.2)	0	0
Accidents and injuries[d]	8 (3.8)	0	0	0	2 (1.0)	0	0	0
Cardiac disorders[c]	3 (1.4)	3 (9.1)	0	0	8 (4.0)	1 (3.0)	0	0
Vascular disorders[c]	26 (12.4)	6 (18.2)	1 (12.5)	0	20 (10.0)	3 (9.1)	1 (20.0)	0
Cerebrovascular disorders[e]	0	0	0	0	0	0	0	0
Infections and infestations[c]	121 (57.9)	16 (48.5)	4 (50.0)	0	73 (36.3)	12 (36.4)	3 (60.0)	0
Anticholinergic syndrome[f]	0	0	0	0	0	0	0	0
Quality of life decreased[g]	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[h]	8 (3.8)	1 (3.0)	0	0	10 (5.0)	1 (3.0)	0	0
Other AE appearing more frequently in older patients								
Abdominal pain	24 (11.5)	7 (21.2)	3 (37.5)	0	20 (10.0)	3 (9.1)	0	0
Decreased appetite	44 (21.1)	10 (30.3)	5 (62.5)	0	35 (17.4)	6 (18.2)	1 (20.0)	0

Treatment-emergent adverse events (TEAE), defined as newly occurring adverse events (not present at baseline) or adverse events that worsen after first dose of study treatment and up through 30 days after the last dose of study treatment, are presented.
For each category or preferred term, multiple occurrences of events within a subject are counted only once.
a. The five chemotherapies are topotecan, vinorelbine, gemcitabine, irinotecan, and pemetrexed.
b. Refers to TEAEs leading to permanent discontinuation of study treatment. c. Based on search of MedDRA SOC term. d. Based on Accidents and injuries SMQ (narrow). e. Based on HLGT Central nervous system vascular disorders. f. Based on Anticholinergic syndrome SMQ (narrow). g. Based on search of preferred terms: Impaired quality of life, Quality of life decreased. h. Based on search of preferred terms: orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, and any preferred term containing the word fracture.
Dictionary: MedDRA v26.0
Data cutoff: 24Jul2023

2.4.8.5. Immunological events

Please refer to the section on clinical pharmacology.

2.4.8.6. Safety related to drug-drug interactions and other interactions

Concomitant use of strong inhibitors of CYP3A4 with tisotumab vedotin has the potential to affect the pharmacokinetics of unconjugated MMAE. Based on clinical data from brentuximab vedotin, concomitant administration of ketoconazole with brentuximab vedotin led to a 34% increase in unconjugated MMAE AUC exposure. The use of inhibitors of CYP3A4 such as ketoconazole with tisotumab vedotin would likely result in similar effects on circulating concentrations of unconjugated MMAE with no change in the pharmacokinetics of ADC exposure.

2.4.8.7. Discontinuation due to adverse events

Table 119 TEAEs Leading to Permanent Treatment Discontinuation in ⩾1Subjects in the SGNTV-003 tisotumab vedotin or Chemotherapy Arm by AESI Category and PT (tisotumab vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Category Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	37 (14.8)	9 (3.8)	14 (13.9)	64 (15.1)	114 (18.2)
Ocular	14 (5.6)	0	6 (5.9)	25 (5.9)	37 (5.9)
Keratitis	6 (2.4)	0	1 (1.0)	7 (1.6)	7 (1.1)
Conjunctivitis	3 (1.2)	0	1 (1.0)	7 (1.6)	13 (2.1)
Symblepharon	2 (0.8)	0	0	2 (0.5)	6 (1.0)
Conjunctival scar	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Corneal degeneration	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Ulcerative keratitis	1 (0.4)	0	3 (3.0)	5 (1.2)	5 (0.8)
Peripheral neuropathy	14 (5.6)	0	6 (5.9)	28 (6.6)	45 (7.2)
Peripheral sensory neuropathy	9 (3.6)	0	3 (3.0)	13 (3.1)	22 (3.5)
Gait disturbance	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Muscular weakness	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Neuralgia	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Neurotoxicity	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Peripheral sensorimotor neuropathy	1 (0.4)	0	2 (2.0)	4 (0.9)	5 (0.8)
Other	9 (3.6)	9 (3.8)	3 (3.0)	13 (3.1)	33 (5.3)
Stevens-Johnson syndrome	2 (0.8)	0	0	2 (0.5)	2 (0.3)
Abdominal pain	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Acute kidney injury	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Asthenia	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Hypertransaminasaemia	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Pneumonia	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Rash macular	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Sepsis	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Cancer pain	0	1 (0.4)	0	0	0
Drug reaction with eosinophilia and systemic symptoms	0	1 (0.4)	0	0	0
Fatigue	0	1 (0.4)	0	0	0
Febrile bone marrow aplasia	0	1 (0.4)	0	0	0
Large intestine perforation	0	1 (0.4)	0	0	0
Pancytopenia	0	1 (0.4)	0	0	0
Septic shock	0	1 (0.4)	0	0	0
Thrombocytopenia	0	1 (0.4)	0	0	0

Multiple occurrences of events within a subject are counted only once. Preferred term of Conjunctival haemorrhage is counted under the Ocular category in this table when applicable.
Within each AESI category, data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 120 TEAEs Leading to Dose Reduction in ⩾1 Subjects in SGNTV-003 tisotumab vedotin Arm by AESI Category and PT (Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Category Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	74 (29.6)	59 (24.7)	23 (22.8)	108 (25.4)	132 (21.0)
Ocular	25 (10.0)	0	20 (19.8)	53 (12.5)	59 (9.4)
Conjunctivitis	10 (4.0)	0	7 (6.9)	21 (4.9)	24 (3.8)
Keratitis	8 (3.2)	0	6 (5.9)	14 (3.3)	14 (2.2)
Punctate keratitis	2 (0.8)	0	2 (2.0)	4 (0.9)	4 (0.6)
Conjunctival erosion	1 (0.4)	0	1 (1.0)	2 (0.5)	2 (0.3)
Conjunctival ulcer	1 (0.4)	0	0	2 (0.5)	4 (0.6)
Dry eye	1 (0.4)	0	3 (3.0)	4 (0.9)	4 (0.6)
Eye oedema	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Lacrimation increased	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Periorbital oedema	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Peripheral neuropathy	24 (9.6)	0	2 (2.0)	26 (6.1)	32 (5.1)
Peripheral sensory neuropathy	17 (6.8)	0	1 (1.0)	18 (4.2)	22 (3.5)
Peripheral motor neuropathy	2 (0.8)	0	0	2 (0.5)	4 (0.6)
Peripheral sensorimotor neuropathy	2 (0.8)	0	1 (1.0)	3 (0.7)	3 (0.5)
Muscular weakness	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Neuralgia	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Neurotoxicity	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Other	31 (12.4)	59 (24.7)	1 (1.0)	35 (8.2)	48 (7.6)
Fatigue	5 (2.0)	1 (0.4)	0	6 (1.4)	8 (1.3)
Decreased appetite	3 (1.2)	0	0	4 (0.9)	4 (0.6)
Weight decreased	3 (1.2)	1 (0.4)	0	3 (0.7)	3 (0.5)
Alanine aminotransferase increased	2 (0.8)	0	0	2 (0.5)	2 (0.3)
Asthenia	2 (0.8)	3 (1.3)	0	2 (0.5)	2 (0.3)
Gastrointestinal toxicity	2 (0.8)	0	0	2 (0.5)	2 (0.3)
Hepatic cytolysis	2 (0.8)	0	0	2 (0.5)	2 (0.3)

Category Preferred Term	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250) n (%)	SGNTV-003 (Pivotal Cervical) Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Neutropenia	2 (0.8)	27 (11.3)	0	2 (0.5)	2 (0.3)
Arthralgia	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Colitis	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Diarrhoea	1 (0.4)	1 (0.4)	0	2 (0.5)	3 (0.5)
Febrile neutropenia	1 (0.4)	2 (0.8)	0	1 (0.2)	2 (0.3)
Hemiparesis	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Hypertransaminasaemia	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Infusion related reaction	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Liver injury	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Nausea	1 (0.4)	0	0	1 (0.2)	2 (0.3)
Pancreatitis	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Small intestinal obstruction	1 (0.4)	0	0	1 (0.2)	1 (0.2)

Multiple occurrences of events within a subject are counted only once. Preferred term of Conjunctival haemorrhage is counted under the Ocular category in this table when applicable.
Within each AESI category, data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Table 121 TEAEs Leading to Dose Interruption in ⩾2 Subjects in SGNTV-003 tisotumab vedotin Arm by AESI Category and PT (Integrated Safety Analysis Set)

Category Preferred Term	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250) n (%)	SGNTV-003 (Pivotal Cervical) Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any event	98 (39.2)	113 (47.3)	48 (47.5)	157 (36.9)	194 (30.9)
Ocular	40 (16.0)	0	10 (9.9)	54 (12.7)	62 (9.9)
Conjunctivitis	22 (8.8)	0	4 (4.0)	27 (6.4)	29 (4.6)
Keratitis	11 (4.4)	0	1 (1.0)	12 (2.8)	12 (1.9)
Punctate keratitis	4 (1.6)	0	1 (1.0)	5 (1.2)	5 (0.8)
Dry eye	2 (0.8)	0	3 (3.0)	5 (1.2)	8 (1.3)
Vision blurred	2 (0.8)	0	0	2 (0.5)	2 (0.3)
Peripheral neuropathy	15 (6.0)	0	8 (7.9)	24 (5.6)	31 (4.9)

Category Preferred Term	SGNTV-003 (Pivotal Cervical) Tisotumab Vedotin (N=250) n (%)	 Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Peripheral sensory neuropathy	12 (4.8)	0	1 (1.0)	13 (3.1)	17 (2.7)
Peripheral sensorimotor neuropathy	2 (0.8)	0	3 (3.0)	5 (1.2)	5 (0.8)
Other	56 (22.4)	112 (46.9)	33 (32.7)	95 (22.4)	119 (18.9)
Urinary tract infection	6 (2.4)	10 (4.2)	2 (2.0)	8 (1.9)	8 (1.3)
COVID-19	5 (2.0)	4 (1.7)	0	5 (1.2)	5 (0.8)
Decreased appetite	4 (1.6)	0	0	4 (0.9)	4 (0.6)
Abdominal pain	3 (1.2)	2 (0.8)	0	3 (0.7)	5 (0.8)
Asthenia	3 (1.2)	5 (2.1)	1 (1.0)	4 (0.9)	4 (0.6)
Fatigue	3 (1.2)	3 (1.3)	0	4 (0.9)	5 (0.8)
Neutropenia	3 (1.2)	28 (11.7)	2 (2.0)	5 (1.2)	7 (1.1)
Alanine aminotransferase increased	2 (0.8)	4 (1.7)	0	3 (0.7)	3 (0.5)
Anaemia	2 (0.8)	25 (10.5)	3 (3.0)	5 (1.2)	6 (1.0)
Hepatic cytolysis	2 (0.8)	0	0	2 (0.5)	2 (0.3)
Vomiting	2 (0.8)	3 (1.3)	1 (1.0)	3 (0.7)	4 (0.6)

Multiple occurrences of events within a subject are counted only once. Preferred term of Conjunctival haemorrhage is counted under the Ocular category in this table when applicable.
Within each AESI category, data are sorted by descending order of frequency and then by ascending alphabetical order of preferred term in 1st column.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

2.4.8.8. Post marketing experience

The initial marketing approval for TIVDAK (tisotumab vedotin) was granted by the FDA on 20-Sep-2021 for the treatment of adult patients with r/mCC with disease progression on or after chemotherapy. Tisotumab vedotin is currently not authorised outside of the US. As of 31-Jul-2023, tisotumab vedotin has been administered to approximately 1500 patients in the post-marketing setting.

All periodic adverse experience reports submitted since initial marketing authorisation in US was granted on 20-Sep-2021 were included in module 5.3.6 (not included in this report). No new safety signals have been identified from post-marketing data sources. Moreover, no SMQs Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) SMQ (narrow), and Torsade de pointes/QT prolongation SMQ (narrow) were reported in the post-marketing setting.

2.4.9. Discussion on clinical safety

The dataset for the safety evaluation of tisotumab vedotin comes from 628 patients, of which 425 patients had cervical cancer. All patients included have received the recommended dose of Tivdak vedotin (TV), i.e. 2.0 mg/kg Q3W. Overall, the size of the safety database is acceptable for a full MA.

The median duration of treatment was 3.65 months and 3.02 months in the TV arm of the pivotal study vs the all tumours pool, respectively. This relatively short exposure is acceptable for the B/R assessment in the current procedure, considering the clinical background and dim prognosis of this disease in the advanced setting. The mean dose intensity of TV was 89-90% across the pools and the median exposure corresponds to the median PFS of the pivotal study (4.2 months). Long-term safety data are not available within this procedure, which is acceptable in view of the targeted setting in advanced late-line cervical cancer. Moreover, final safety data from the pivotal study SGNTV-003 is included in the RMP as Category 3 study and will be provided as post-authorisation measure.

Almost all of the patients treated with TV experienced at least one adverse event (AE), 98.4% in the TV arm of study SGNTV-003 vs. 98.7% in the all tumour types pool (ATT pool). The majority of the events were considered treatment-related by investigators. More than half of the patients had a grade ≥3 AE (52% vs 55.9%), of which ~30% were considered treatment-related (29.2% vs 31.7%).

The most common adverse events (>25%) reported in the TV arm were nausea, conjunctivitis, peripheral sensory neuropathy, and epistaxis. The grade ≥ 3 events commonly observed of Subjects in the SGNTV-003 were anaemia (8.4%), urinary tract infection (4.4%), abdominal pain (4%), and neutropenia (3.6%).

The most common treatment-related AEs in the TV arm of Subjects in the SGNTV-003 were conjunctivitis, nausea, peripheral sensory neuropathy, alopecia, and epistaxis.

Less treatment-related peripheral neuropathy was observed in the ATT pool, which may reflect less accumulated toxicity from previous treatments in this group, in comparison with the relevant cervical cancer group, who often have received prior cisplatin and taxanes prone to causing peripheral neuropathy.

More treatment-related epistaxis events were observed in the ATT pool (35.2% vs 22.8%) and the risk of bleeding will be further discussed below.

Treatment-related grade 3 or higher adverse events were quite common, and most often events observed in the TV arm were anaemia, fatigue, neutropenia (3.6% each), peripheral sensory neuropathy (2.8%) and keratitis (2.8%).

In comparison, the most commonly observed AEs with chemotherapy of Subjects in the SGNTV-003 were anaemia (52.3%), nausea (40.2%), and neutropenia (22.6%). The grade ≥3 events were anaemia (27.6%), neutropenia (13.4%), and urinary tract infection (7.1%). In addition, skin adverse events such as alopecia, rash and pruritus are commonly seen with other Antibody Drugs Conjugated. GI disorders and haematological toxicity and associated infections may be related to release of cytotoxic payloads into blood circulation and are frequently observed for ADCs with MMAE. Gastrointestinal disorders (e.g., obstruction of the gastrointestinal tract), and adverse events in the genito-urinary tract may be disease-relate. GI disorders can be considered ADRs.

Even though frequencies of haemato-toxicities are less frequent with TV treatment than with chemotherapy, they are still a major safety concern. Anaemia and neutropenia are particularly notable and are regarded as linked to the treatment. Moreover, infections PTs, except for conjunctivitis, happen at similar rates as with chemotherapy, which is known to increase infection risk. While anaemia might be related to the disease, it's less clear for neutropenia. The exposure-safety analyses for

tisotumab vedotin (ADC) and unconjugated MMAE for several haematological or infection AEs provided suggests no clear link between exposure and safety, however it's unclear if these results definitively rule out a causal relationship. There seems to be a possible class effect when also examining the safety profile of other ADCs. Since anaemia and neutropenia have been observed in non-clinical studies and severe clinical cases have been observed, these AEs are considered ADRs for tisotumab vedotin.

Adverse events of special interest:

Ocular toxicity of TV appears to be distinct from other ADCs., were the ocular TEAEs were confined to the ocular surface possibly due to tissue factor (TF)-directed delivery of MMAE within the conjunctiva and cornea. More than half of the patients in the pivotal study had ocular toxicity of any grade (52.8%), while ~5.3% had grade 3 or more events of ocular toxicity. In the ATT pool, the any grade incidence was 56.2% and ~3.7% had grade 3 or more events of ocular toxicity. The time to onset was median 1.2 months and the median time to resolution was 0.58 months.

As a consequence of the ocular toxicity, prior to the first infusion and as clinically indicated, patients should be referred to an eye care professional for a full eye exam (including visual acuity and slit lamp exam). Prior to each infusion, the treating healthcare provider should inspect the patient's eyes, including control of normal eye movement, and ask about any ocular signs or symptoms. Patients should be monitored for new or worsening ocular signs and symptoms and referred as soon as possible to an eye care professional if warranted. Patients should be instructed to promptly report any new or worsening ocular signs or symptoms. TV should be withheld, dose reduced, or permanently discontinued based on the severity of the adverse reaction (see sections 4.2, 4.4 and 4.8 of the SmPC).

In addition, patients should adhere to the following recommendations to reduce the risk of ocular adverse reactions:

- Patients should be instructed to administer 1 drop of topical preservative-free corticosteroid (e.g., dexamethasone 0.1% 3 times a day or the equivalent as prescribed) in each eye 3 times daily starting 1 day prior to each infusion and to continue to administer as prescribed for 3 days after each infusion.

- Topical preservative-free ocular vasoconstrictor Drops (e.g., brimonidine tartrate 0.2% 3 drops per eye or the equivalent as prescribed) should be administered in each eye immediately prior to each infusion.

- Following administration of eye drops, cooling eye pads should be applied prior to the start of the infusion and used during and for 30 minutes after the infusion.

- Patients should be instructed to administer topical preservative-free lubricating eye drops multiple times every day throughout treatment and for 30 days after the last dose of TV.

- Patients should be advised to avoid wearing contact lenses for the entire duration of therapy unless advised by their eye care professional.

Peripheral neuropathy is a known safety risk of tisotumab vedotin treatment as the cytotoxic component of the ADC, MMAE, is a microtubule-disrupting agent. More than a third of the patients in the pivotal study had peripheral neuropathy of any grade (38.7%) in the pivotal study, SAEs were rare (1.2% and 2.2%, respectively), but it is noted that 5.6% and 7.2% had to discontinue treatment due to peripheral neurotoxicity in the pivotal study and the ATT pool, respectively. Most often the events were sensory in nature with the most frequently reported events being peripheral sensory neuropathy and paraesthesia. The median time to onset of peripheral neuropathy was 2.7 months and the mean time to resolution was 1.85 months in the pivotal study. Only a quarter of the patients had all events resolved (25.2%).Overall, the peripheral neuropathy from TV is considered very common, chronic in

nature and although rarely of grade 3 or more, the events were not resolvable for the majority of the patients and led to treatment discontinuation in almost 6% of the patients.

Patients should be monitored for general symptoms of neuropathy, such as paraesthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. Patients experiencing new or worsening peripheral neuropathy may require dose interruption, dose reduction, or permanent discontinuation of TV (see sections 4.2, 4.4 and 4.8 of the SmPC).

Bleeding events were very commonly observed with TV in comparison to chemotherapy as any bleeding event was observed in 42% in the TV arm, 14% in the chemotherapy arm and in 54.5% in the ATT pool. Grade 3 and serious adverse events (SAEs) were rare, and 2% and 4% had a grade 3 event in the TV arm vs the ATT pool, respectively. The most frequent bleeding sites were from the nose, vagina or the urinary tract. In the TV arm vs the ATT pool, respectively, the incidences were: epistaxis (26% and 40.1%), vaginal bleeding (10% and 7.3%), and haematuria (7.2% vs 6.8%). The mean time to onset was 1.3 months and 0.83 months, in the TV arm and the ATT pool, respectively, while approximately 80% of the events overall were resolved or resolved with sequelae at DCO.

Although bleeding events were observed more frequently with tisotumab vedotin in comparison to the chemotherapy arm, the difference was driven mostly by grade 1-2 events, while the frequency of high-grade and serious adverse events were similar between the arms (2.4% vs 2.9%). Epistaxis was the most common bleeding event (26.0% in the TV arm vs 2.5% in the chemotherapy arm). All events of epistaxis in the TV arm were non-serious and mostly grade 1 (24.8%), which is self-limited and did not require intervention. No Grade 3 or higher epistaxis were reported and most events had improved or resolved in approximately 2 weeks (81.5%).

The high-grade bleeding events observed were mainly bleeding at the location of the tumour, mostly related to the underlying advanced disease pathophysiology and/or progression, since bleeding is associated with tumour infiltration into surrounding tissues. The high-grade bleeding events were manageable with standard supportive care (e.g., transfusions).. Dose interruptions due to bleeding were similar in both arms (0.8%); none of the patients needed dose reduction nor treatment discontinuations due to bleeding and no fatal bleedings were observed. This is reassuring and supports that the events were manageable.Epistaxis is included as an ADR in section 4.8 of the SmPC.

Serious adverse events (SAEs) occurred in 32.8% of patients in the TV arm vs 39.3% in the chemotherapy arm of the pivotal study SGNTV-003 and in 38.7% in the ATT pool. The most common SAEs with TV were urinary tract infection (UTI), small bowel obstruction, abdominal pain and sepsis. In the chemotherapy arm, most common SAEs were urinary tract infection, anaemia and febrile neutropenia. Treatment-related SAEs were observed in 10% in the TV arm vs 14.6% in the chemotherapy arm vs 15% in the ATT pool. The related SAEs with TV were fatigue, vomiting and neutropenia. Severe GI tract AEs with tisotumab vedotin occur relatively frequently and this information is included in SmPC.

It is also suggested in literature that ADCs may increase the risk of sepsis (Xia et al. Front Pharmacol. 2022). When examining SAEs, sepsis was reported in a slightly higher frequency in the tisotumab vedotin arm compared to the chemotherapy arm (2.0% vs 0.8%, respectively).

Deaths were observed in 12 patients (4.8%) in the TV arm vs 7.5% in the chemotherapy arm of the pivotal study and in 5.1% in the ATT pool. The most common reasons were disease-related or due to an adverse event. In the TV arm, 4 patients died from an adverse event; 1 from acute kidney injury, 1 pneumonia, 1 sepsis and 1 from Steven-Johnson syndrome. In the ATT pool, 7 patients died from an adverse event; 1 from acute kidney injury, 1 pneumonia, 1 sepsis + 1 septic shock; 1 from Steven-Johnson syndrome, 1 unknown and 1 from worsening of cervical cancer. Most of patients who died, died from progressive disease.

Considering the risk of fatal or life threatening SJS, Patients should be monitored for signs or symptoms of severe cutaneous adverse reactions, which include target lesions, worsening skin reactions, blistering or peeling of the skin, painful sores in mouth, nose, throat, or genital area, fever or flu like symptoms, and swollen lymph nodes. If signs or symptoms of severe cutaneous adverse reactions occur, TV should be immediately withheld until the aetiology of the reaction has been determined. Early consultation with a specialist is recommended to ensure greater diagnostic accuracy and appropriate management. TV should be permanently discontinued for confirmed Grade 3 or 4 severe cutaneous adverse reactions, including SJS (see sections 4.2, 4.4 and 4.8 of the SmPC).

Significantly more patients **discontinued treatment** in the TV arm (14.8 % vs 3.8%), while it was 18.2% in the ATT pool. The most common AEs leading to discontinuation of TV were: ocular events, peripheral neuropathy and other, both in the TV arm and the ATT pool. The level of discontinuations of TV is on the edge, meaning that these numbers are lower than what would probably be observed in the patient population with advanced cervical cancer outside of a clinical trial setting.

Laboratory findings showed that haematological toxicity was common with TV, mostly in grade 1 or 2 and no grade 4 or 5 events were observed. Liver parameters were commonly increased of grade 1-2 with TV, and most often AST, ALT and alkaline phosphatase was increased. Grade 3 and 4 events of increased liver parameters were rarely observed with TV; and the coagulation parameters were affected of grade 1-2 with TV, especially APTT and INR. The applicant has clarified that there was no relation between affected coagulation and bleeding events in the pivotal study. Clinical chemistry parameters were affected to a similar degree with both TV and chemotherapy and of an acceptable level.

2.4.10. Conclusions on the clinical safety

The safety profile of tisotumab vedotin derived from the data of 628 patients treated with TV,for an adequate exposure period. The safety profile of TV was compared head-to head with chemotherapy, which is the standard of care in the targeted second-line advanced treatment setting of cervical cancer. Overall, the toxicities observed with TV are considered significantly different from those observed with chemotherapy and the tolerability of TV appears to be lower.

The following measures are necessary to address the missing safety data in the context of a full MA:

Final safety data from the pivotal study SGNTV-003 will be provided as post-authorisation measure and is listed as category 3 study in the RMP.

2.5. Risk Management Plan

The RMP assessed is the version 0.4 with data lock 24 July 2023.

2.5.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 122: Summary of safety concerns

Summary of safety concerns	
Important identified risks	*Severe Ocular AEs* *Peripheral neuropathy*

	SCAR/SJS
Important potential risks	*QTc prolongation*
Missing information	*Long term safety*

2.5.2. Pharmacovigilance plan

Table 123 Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)(by the competent authority)				
C5721002 (SGNTV-003; innovaTV301) Ongoing Category 3	Evaluate the safety and tolerability of tisotumab vedotin and chemotherapy in participants with second- or third-line (2L3L) cervical cancer	Long term safety	Final study report submission	Projected Q4 2027

Risk minimisation measures

Table 124: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Severe ocular toxicity	Routine risk minimisation measures: • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
Peripheral neuropathy	Routine risk minimisation measures: • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
SCARs/SJS	Routine risk minimisation measures: • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
Important Potential Risks:		
QT prolongation	Routine risk minimisation measures: • Prescription only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information		
Long term safety	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study C5721002 (SGNTV-003)

2.5.3. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6

(as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20-Sept-2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tivdak (Tisotumab vedotin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final agreed indication is:

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy (see section 5.1).

3.1.2. Available therapies and unmet medical need

Patients who have progressed after 1L treatment have limited effective subsequent treatment options. Based on results from the EMPOWER Cervical 01 trial (also known as Study 1676), patients who were not previously exposed to checkpoint inhibitors can be offered cemiplimab (EMEA/H/C/004844-II-0026) (Tewari 2022). Other options are single drug regimens (e.g. gemcitabine, vinorelbine, topotecan), which have low response rates and variable chemotherapy-related toxicity (Marth 2017).

An unmet medical need remains as there are limited treatment options in the 2L and beyond setting and the prognosis for these patients is dismal.

3.1.3. Main clinical studies

The current application is based on the results of study SGNTV-003 (also known as innovaTV 301), an open-label, randomised 1:1, phase III trial that compared tisotumab vedotin monotherapy vs. investigator's predefined choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in women with recurrent or metastatic cervical cancer after progression on doublet chemotherapy with or without bevacizumab and anti-PD(L)1 inhibitor. 502 patients were randomised 1:1 to the tisotumab vedotin (253) and chemotherapy (249). The primary endpoint was overall survival (OS). Secondary endpoints were investigator-assessed PFS, ORR, DOR and TTR.

3.2. Favourable effects

At the cut-off date for primary analysis of 24 July 2023 and with a median duration of follow-up of 10.8 months, the primary endpoint, OS benefit with tisotumab vedotin vs investigator's choice of chemotherapy (52% of OS maturity) was met. A statistically significant OS advantage of tisotumab vedotin vs chemotherapy was shown with a HR of 0.70 (0.54, 0.89), p-value 0.0038 and median OS improvement of 2 months (median OS 11.5 months in tisotumab vedotin arm vs 9.5 months in chemotherapy arm). The OS benefit was observed in nearly all predefined clinically relevant subgroups.

Secondary endpoint of PFS by Investigator (78% of PFS maturity) was also statistically significant with HR 0.67 (0.54,0.82); p-value <0.0001 and improvement of 1.3 months of PFS (median PFS 4.2 months in tisotumab vedotin arm vs. 2.9 months in chemotherapy arm). In addition, an improvement in ORR (17.8% vs. 5.2%, Odds Ratio 4.0, p-value <0.0001) was observed. Six patients (2.4%) in the tisotumab vedotin arm vs. 0 in the chemotherapy arm achieved CR as the best confirmed response.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

In study SGNTV-003, 98.4% of the patients treated with TV experienced at least one adverse event (AE) vs. 98.7% in the all tumour types pool (ATT pool).

The most common **adverse events** (>25%) reported in the TV arm were nausea, conjunctivitis, peripheral sensory neuropathy, and epistaxis. The grade ≥ 3 events commonly observed were anaemia (8.4%), urinary tract infection (4.4%), abdominal pain (4%), and neutropenia (3.6%).

The most common **treatment-related** AEs in the TV arm were conjunctivitis, nausea, peripheral sensory neuropathy, alopecia, and epistaxis and **grade 3 or higher adverse events** in the TV arm were anaemia, fatigue, neutropenia (3.6% each), peripheral sensory neuropathy (2.8%) and keratitis (2.8%).

In comparison, the most commonly observed **AEs with chemotherapy** were anaemia (52.3%), nausea (40.2%), and neutropenia (22.6%). The grade ≥3 events were anaemia (27.6%), neutropenia (13.4%), and urinary tract infection (7.1%).

Adverse events of special interest includes ocular toxicity and peripheral neurotoxicity, both of which are important identified risks with TV in the RMP. **Bleeding** events were very commonly observed with TV in comparison to chemotherapy.Any bleeding event was observed in 42% in the TV arm, in 14% in the chemotherapy arm and in 54.5% in the ATT pool. Severe cutaneous adverse reaction (SCAR) was reported in 2.4% of the patients in the TV arm, of which one Grade 5 event. Grade 3 and serious adverse events (SAEs) were rare, and 2% and 4% had a grade 3 event in the TV arm vs the ATT pool, respectively.

Deaths were observed in 12 patients (4.8%) in the TV arm vs 7.5% in the chemotherapy arm of the pivotal study and in 5.1% in the ATT pool. The most common reasons were disease-related or due to an adverse event.

Significantly more patients **discontinued treatment** in the TV arm compared to the chemotherapy arm (14.8 % vs 3.8%), while it was 18.2% in the ATT pool. The most common AEs, both in the TV arm and the ATT pool.. leading to discontinuation of TV were ocular events and peripheral neuropathy.,.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety data from tisotumab vedotin are not available at present, but final safety data from the pivotal study SGNTV-003 will be provided as a recommendation post-authorisation.

Most of the patients who died, died from progressive disease. However, three treatment-related death were observed (due to acute kidney injury worsened by possibly related diarrhoea, SJS and sepsis) and are reported in the SmPC.

Patients were excluded from the study, if they had active ocular surface disease, cicatricial conjunctivitis or ocular SJS, Grade ⩾2 peripheral neuropathy, or known coagulation defects or events leading to an increased risk of bleeding or cardiovascular risks. It is therefore not known if a similar safety profile would have been observed, had these patients been included in the study. Special warnings and precautions for use for these ADRs are included in section 4.4 of the SmPC.

3.6. Effects Table

Table 125: Effects Table for Tivdak vedotin for advanced cervical cancer (data cut-off: 24 July 2023).

Effect	Short Description	Unit	Treatment Tisotumab vedotin N=253	Control Chemotherapy N=249	Uncertainties / Strength of evidence	Ref
Favourable Effects						

Effect	Short Description	Unit	Treatment Tisotumab vedotin N=253	Control Chemotherapy N=249	Uncertainties / Strength of evidence	Ref
OS	Overall survival	Events n (%) Median OS (months) 95% CI	123 (48.6) 11.5 (9.8, 14.9)	140 (56.2) 9.5 (7.9, 10.7)	Median follow-up 10.8 months OS maturity	CSR
		HR (95% CI) p-value	0.70 (0.54, 0.89) 0.0038			
PFS INV	Progression-free survival	Events n (%) Median PFS (months) 95%CI	198 (78.3) 4.2 (4.0, 4.4)	194 (77.9) 2.9 (2.6, 3.1)	Investigator-assessed secondary endpoints	
		HR (95% CI) p-value	0.67 (0.54, 0.82) <0.0001			
ORR INV	Overall response rate	CR+PR n (%) 95%CI	45 (17.8) (13.3, 23.1)	13 (5.2) (2.8, 8.8)		
DOR	Duration of response	Median (months) 95%CI	5.3 (4.2, 8.3)	5.7 (2.8, NR)		
Unfavourable Effects in the pivotal study SGNTV-03 (n=250 TV, n= 239 Chemotherapy)						
Grade ⩾3 AEs		%	52.0	62.3		
SAEs		%	32.8	39.3		
AEs leading to disc.		%	14.8	3.8		
AEs leading to death		%	1.6	2.1		
Ocular toxicity		%	52.8	6.3		
Peripheral neuropathy		%	38.4	4.2		
Bleeding events		%	42.0	14.2		

Abbreviations: INV- Investigator; AEs – adverse events; SAEs – serious adverse events.

Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The overall efficacy outcome of this pivotal trial is positive and showed efficacy benefits from tisotumab vedotin across all important endpoints (OS, PFS, ORR) over Investigator's choice of chemotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.

The safety profile of tisotumab vedotin was compared head-to head with chemotherapy. Overall, the toxicities observed with tisotumab vedotin are considered significantly different from those observed

with chemotherapy and the tolerability of tisotumab vedotin appears to be lower expressed by the higher rates of discontinuations. Considering the serious toxicities with tisotumab vedotin, including treatment-related deaths, long-term safety data is considered needed to further characterise the time to resolution or chronicity of the adverse drug reactions observed. Therefore, the final safety data from the pivotal study SGNTV-003 is included in the RMP as Category 3 study and will be submitted post-authorisation **(PAM).**

3.6.2. Balance of benefits and risks

The statistically significant improvement in OS and PFS observed with tisotumab vedotin compared with chemotherapy outweighs the risks identified in patients with recurrent/metastatic cervical cancer who progressed after systemic therapy, for whom the treatment options are limited.

3.6.3. Additional considerations on the benefit-risk balance

None

3.7. Conclusions

The overall benefit /risk balance of Tivdak (tisotumab vedotin) in the agreed indication is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Tivdak is favourable in the following indication:

Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy (see section 5.1).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that tisotumab vedotin is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.