Tisotumab vedotin in patients with advanced or metastatic solid tumours (InnovaTV 201): a first-in-human, multicentre, phase 1–2 trial

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Summary

Background Tisotumab vedotin is a first-in-human antibody–drug conjugate directed against tissue factor, which is expressed across multiple solid tumour types and is associated with poor clinical outcomes. We aimed to establish the safety, tolerability, pharmacokinetic profile, and antitumour activity of tisotumab vedotin in a mixed population of patients with locally advanced or metastatic (or both) solid tumours known to express tissue factor.

Methods InnovaTV 201 is a phase 1–2, open-label, dose-escalation and dose-expansion study done at 21 centres in the USA and Europe. Patients (aged ≥18 years) had relapsed, advanced, or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, oesophagus, squamous cell carcinoma of the head and neck or non-small-cell lung cancer; an Eastern Cooperative Oncology Group performance status of 0–1; and had relapsed after or were not eligible to receive the available standard of care. No specific tissue factor expression level was required for inclusion. In the dose-escalation phase, patients were treated with tisotumab vedotin between 0·3 and 2·2 mg/kg intravenously once every 3 weeks in a traditional 3+3 design. In the dose-expansion phase, patients were treated at the recommended phase 2 dose. The primary endpoint was the incidence of adverse events, including serious adverse events, infusion-related, treatment-related and those of grade 3 or worse, and study drug-related adverse events, analysed in all patients who received at least one dose of tisotumab vedotin (full analysis population). This trial is registered with ClinicalTrials.gov, number NCT02001623, and is closed to new participants with follow-up ongoing.

Findings Between Dec 9, 2013, and May 18, 2015, 27 eligible patients were enrolled to the dose-escalation phase. Dose-limiting toxicities, including grade 3 type 2 diabetes mellitus, mucositis, and neutropenic fever, were seen at the 2·2 mg/kg dose; therefore, 2·0 mg/kg of tisotumab vedotin intravenously once every 3 weeks was established as the recommended phase 2 dose. Between Oct 8, 2015, and April 26, 2018, 147 eligible patients were enrolled to the dose-expansion phase. The most common (in ≥20% of patients) treatment-emergent adverse events of any grade were epistaxis (102 [69%] of 147 patients), fatigue (82 [56%]), nausea (77 [52%]), alopecia (64 [44%]), conjunctivitis (63 [43%]), decreased appetite (53 [36%]), constipation (52 [35%]), diarrhoea (44 [30%]), vomiting (42 [29%]), peripheral neuropathy (33 [22%]), dry eye (32 [22%]), and abdominal pain (30 [20%]). The most common adverse events of grade 3 or worse were fatigue (14 [10%] of 147 patients), anaemia (eight [5%]), abdominal pain (six [4%]), hypokalaemia (six [4%]), conjunctivitis (five [3%]), hyponatraemia (five [3%]), and vomiting (five [3%]). 67 (46%) of 147 patients had a treatment-emergent serious adverse event. 39 (27%) of 147 patients had a treatment-emergent serious adverse event related to the study drug. Infusion-related reactions occurred in 17 (12%) of 147 patients. Across tumour types, the confirmed proportion of patients who achieved an objective response was 15·6% (95% CI 10·2–22·5; 23 of 147 patients). There were nine deaths across all study phases (three in the dose-escalation phase and six in the dose-expansion phase); only one case of pneumonia in the dose-expansion phase was considered possibly related to study treatment.

Interpretations Tisotumab vedotin has a manageable safety profile with encouraging preliminary antitumour activity across multiple tumour types in heavily pretreated patients. Continued evaluation of tisotumab vedotin is warranted in solid tumours.

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Introduction

Tisotumab vedotin is a first-in-human antibody–drug conjugate that is directed against tissue factor expressed on the cell surface of tumour cells to deliver a clinically validated toxic payload to tumours.[1,2] Tisotumab vedotin is comprised of a fully human monoclonal antibody specific for tissue factor conjugated to the microtubule-disrupting agent monomethyl

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Research in context

Evidence before this study

We searched PubMed from inception to Aug 19, 2018, for all clinical studies evaluating the use of tissue factor-targeting therapeutics in patients with cancer, using the following search terms: "tissue factor" OR "thromboplastin" OR "CD142." Tissue factor is broadly expressed across multiple solid tumour types and contributes to cancer biology by promoting metastasis, tumour growth, and tumour angiogenesis, suggesting that it could be a target for therapeutic intervention. Our search showed that no studies have been published on the safety and activity of tissue factor-targeting agents in patients with cancer, although two early phase clinical trials evaluated this type of drug in patients with macular degeneration or acute lung injury.

Added value of this study

To our knowledge, this is the first study assessing the safety, tolerability, pharmacokinetics, and preliminary activity of a tissue factor-targeting agent, tisotumab vedotin, in patients with cancer. In this phase 1–2 study, tisotumab vedotin showed a manageable safety profile and preliminary activity in patients with advanced solid tumours, including those with bladder, cervical, endometrial, oesophageal, lung, and ovarian cancer.

Implications of all the available evidence

The prognosis for patients with advanced solid tumours is poor and there is an unmet need for new treatments to improve outcomes. Our study shows the feasibility and preliminary clinical activity of tisotumab vedotin, and further studies are now required to confirm this activity and assess in which patients tisotumab vedotin is most likely to be effective.

auristatin E (MMAE) via a protease-cleavable valine-citrulline linker.[1]

Tissue factor is a transmembrane glycoprotein that functions as the main initiator of the tissue factor pathway of blood coagulation, also known as the extrinsic coagulation pathway.[3,4] Beyond its function in coagulation, tissue factor has cell-signalling properties.[5] In complex with its physiological ligand FVIIa, tissue factor can activate protease-activated receptor 2, resulting in an intracellular signalling cascade that tumours can exploit to promote malignant cell survival, tumour growth, angiogenesis, and metastasis.[3,5,6] The role of tissue factor in cancer biology is underscored by its aberrant expression in various solid tumours. For example, high percentages of tissue factor-positive tumour biopsies, as assessed by immunohistochemistry, were seen in cervical cancer (100%), non-small-cell lung cancer (34–88%), endometrial cancer (14–100%), prostate cancer (47–75%), ovarian cancer (75–100%), oesophageal cancer (43–91%), and bladder cancer (78%).[7–18] Expression of tissue factor is enhanced in cancer through oncogenic events, such as constitutive activation of the MAPK and PI3K signalling pathways, hypoxia-induced signalling, and loss of tumour suppressor genes.[3] Tissue factor expression has been associated with poor clinical outcomes and increased metastatic potential in several types of solid tumours, including those of the pancreas and bladder.[6,18,19] Treatment options for many of these solid tumours are restricted, especially in the context of metastatic and refractory disease, and are often hampered by poor efficacy or substantial toxicities, or both. More effective and tolerable treatment alternatives are urgently needed for patients with these types of cancer and advanced disease. Given its differential expression in many cancers and its role in cancer biology, tissue factor is a rational target for the development of therapeutics to help to address this unmet need and the potential to improve patient outcomes across a range of solid tumours.

The antibody moiety of tisotumab vedotin (also known as HuMax-tissue factor) was selected from a panel of tissue factor-specific human monoclonal antibodies on the basis of its high affinity binding to tissue factor (low nM range) and its capacity for interfering with protease activated receptor 2 intracellular signalling, as assessed by inhibition of tissue factor: FVIIa-dependent ERK phosphorylation and interleukin-8 production in tissue factor-positive tumour cells. In-vitro internalisation studies showed that tisotumab vedotin was efficiently internalised upon binding to tissue factor-positive tumour cells. Tisotumab vedotin had little effect on tissue factor procoagulant activity in vitro, as assessed by a chromogenic FXa generation assay and thrombo-elastography analysis.[1] Notably, tisotumab vedotin, which had similar binding to that of human and cynomolgus monkey tissue factor, did not induce clear effects on parameters of coagulation at high doses (up to 100 mg/kg) in cynomolgus monkeys. Tisotumab vedotin induces potent cytotoxicity in tissue factor-positive tumour cells in vitro and was shown to be the most potent of three different tissue factor-specific MMAE-based antibody–drug conjugates in preclinical murine xenograft tumour models in vivo.[1] The dominant mechanism of action of tisotumab vedotin in preclinical models was MMAE-mediated tumour cell killing. Upon binding of tissue factor by tisotumab vedotin, the resulting complex is internalised and trafficked to the lysosome where the linker is enzymatically cleaved, releasing MMAE within the targeted tumour cell.[1,20] MMAE then binds to tubulin and disrupts microtubule polymerisation, resulting in G2/M cell cycle arrest and apoptosis.[1,21] As a cell-permeable molecule, MMAE can also diffuse into the tumour microenvironment, where it might induce

bystander killing of neighbouring dividing cells.[1,20] These antitumour effects are further enhanced by the capacity of tisotumab vedotin to bind FcγRIIIa on adjacent natural killer cells, which leads to antibody-dependent cellular cytotoxicity of tissue factor-expressing tumour cells.[1,22] MMAE-based antibody–drug conjugates have also been shown to induce immunogenic cell death, which can activate innate and adaptive immune responses to tumour antigen.[23] In preclinical studies, tisotumab vedotin had robust antitumour activity in vitro and in xenograft models in vivo, using models derived from multiple solid tumours, including bladder, prostate, lung, pancreas, ovarian, and cervical, which showed differential expression of tissue factor.[1]

InnovaTV 201 is the first-in-human clinical trial of tisotumab vedotin. We studied patients with tumour types that are known to express tissue factor and are susceptible to microtubule-disrupting agents.

Methods

Study design and participants

InnovaTV 201 was a phase 1–2, open-label, multicentre, dose-escalation, and dose-expansion study. We recruited patients across three sites (Denmark, UK, and USA [one each]) for the dose-escalation phase and 21 sites (Belgium, six; Denmark, two; Sweden, one; UK, nine; USA, three) for the dose-expansion phase (appendix p 2).

Eligible patients were aged 18 years or older; had advanced or metastatic solid tumours; a life expectancy of at least 3 months; acceptable organ function, haematological, and coagulation status; Eastern Cooperative Oncology Group performance status of 0 or 1; measurable disease according to Response Evaluation Criteria in Solid Tumours (version 1.1); and relapsed after or were not eligible to receive the available standard of care.[24] The patient population in the dose-escalation phase included patients with cancer of the ovary, cervix, endometrium, bladder, prostate, oesophagus, non-small-cell lung cancer, or squamous cell carcinoma of the head and neck. In the cohort expansion phase, patients with cancer of the ovary, cervix, endometrium, bladder, prostate, oesophagus, and non-small-cell lung cancer were included. Patients with prostate cancer 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. All patients were required to have a tumour biopsy at screening. A fresh biopsy was collected at least 2 weeks before dosing, if no archival tissue was available. There were no requirements for tumour tissue factor expression for eligibility.

Patients were excluded if they had previous or current coagulation defects, ongoing major bleeding, long-term antiplatelet or anticoagulant therapy, clinically significant cardiac disease, major surgery within 6 weeks before drug infusion or anticipated during study treatment, open biopsy within 7 days before drug infusion, had another malignancy or known infection with HIV, hepatitis B virus, or hepatitis C virus, or had received prior therapy with an auristatin derivative, bevacizumab within 12 weeks from first study dose, radiotherapy within 28 days from first study dose, or any other anticancer therapy within five half-lives before first dose. The complete eligibility criteria are in the protocol (appendix p 11).

The study protocol was amended on Dec 22, 2016 and June 23, 2017, to implement ocular preventive measures after 77 patients were enrolled; measures included the use of lubricating eye drops throughout the study period, steroid eye drops during the first 3 days of each treatment cycle, local ocular vasoconstrictor before treatment infusion, cooling eye masks worn during treatment infusion, and stricter guidance on dose adjustment.

The independent ethics committee or institutional review board at each study site approved the protocol, and the study was done in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent for participation.

Procedures

We used a traditional 3+3 design for the dose-escalation phase. Non-clinical safety studies were done in cynomolgus monkeys that were treated with tisotumab vedotin at 1–5 mg/kg in a 13-week repeat dose toxicity study (dosing once every 3 weeks for five cycles). In this study, 3 mg/kg was the highest dose associated with an acceptable safety profile. Based on these data and taking into account a safety factor of 10, we set the first-in-human dose at 0·3 mg/kg. Based on adverse events observed in these studies—especially reversible bone marrow toxicity and low neutrophil counts that showed a nadir between 10 and 18 days after treatment—the dosing schedule of once every 3 weeks was selected. Patients were enrolled to eight cohorts of tisotumab vedotin, ranging from 0·3 to 2·2 mg/kg administered intravenously once every 3 weeks. The decision to proceed to the next dose level in the dose-escalation phase was made on the basis of the rate of dose-limiting toxicities seen during the first 21-day treatment cycle. The dose below the dose at which two or more dose-limiting toxicities occurred within six patients was defined as the maximum tolerated dose and the recommended phase 2 dose.

See Online for appendix

We used a multiple cohort design for the dose-expansion phase of the study and enrolled patients in cohorts defined by tumour type to be treated with tisotumab vedotin at the recommended phase 2 dose. Patients were treated for up to four cycles or until disease progression. Recruitment was initiated in five tumour cohorts, including bladder, cervix, endometrium, ovary, and prostate. Following a safety review on March 24, 2016, from the ten first patients recruited and followed for at least one cycle, regardless of indication, recruitment for the lung and oesophageal cohorts started. Patients who

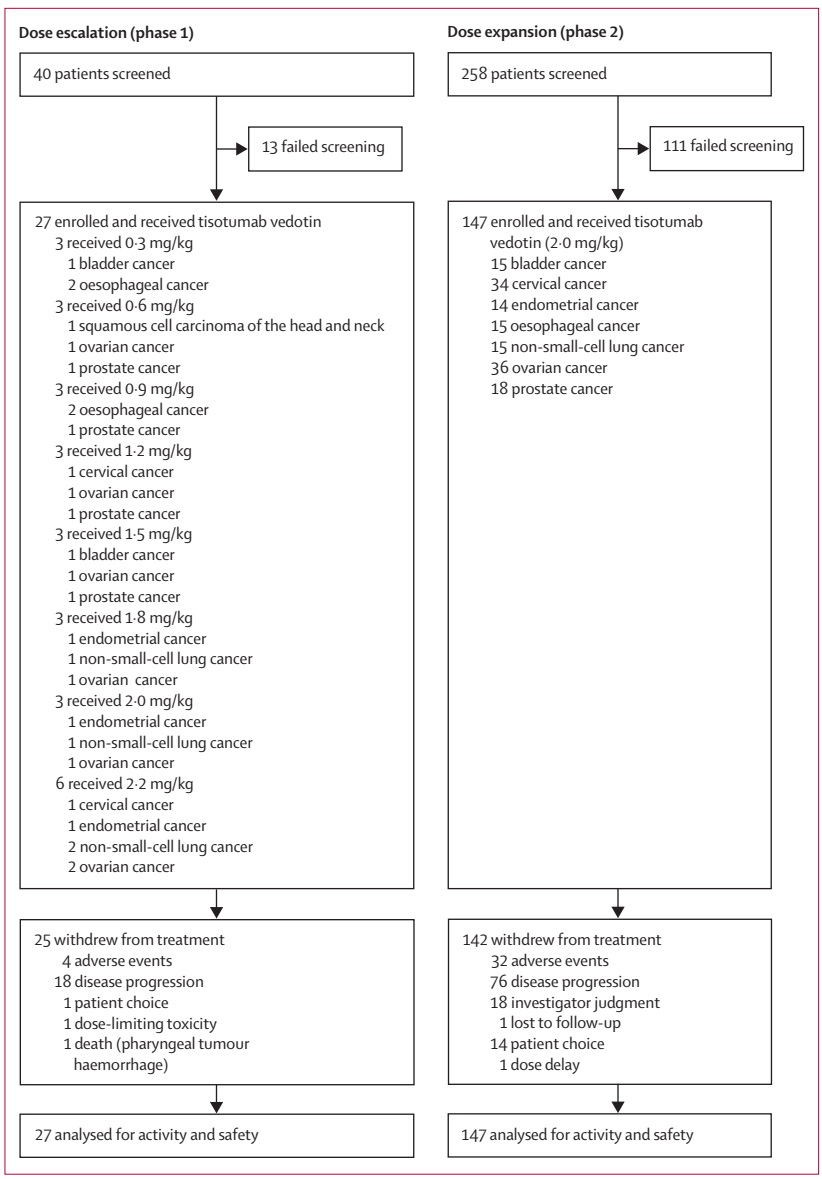

Figure 1: **Trial profile**

showed clinical benefit, defined as stable disease or better, had the option to continue treatment for an additional eight cycles or until unacceptable toxicity or disease progression.

Adverse events were assessed and reported at each visit according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4·03. All patients received study treatment; therefore, all adverse events, regardless of causality, were considered treatment-emergent adverse events. Investigators used their own judgment to determine whether or not the treatment-emergent adverse event was related to the study drug. Safety laboratory parameters and safety events of interest, including skin disorders, bleeding events, and neuropathy were included in the safety analysis. A data monitoring committe evaluated safety data during the study.

Dose-limiting toxicities were defined per protocol (appendix p 11). Causality for dose-limiting toxicities was assessed by the investigators and sponsor in collaboration with the data monitoring committee.

Tumour response was assessed by investigators according to Response Evaluation Criteria in Solid Tumours (version 1.1) at screening and every 6 weeks during the study, done with the use of CT or by MRI in patients who were allergic to iodine contrast or at the discretion of the investigator. Changes in prostate-specific antigen were monitored in patients with prostate cancer, and changes in cancer antigen 125 in patients with ovarian cancer.

Blood samples for pharmacokinetic analysis were collected before and after the infusion at each cycle. Additional samples were collected during cycles 1 and 2 on day 1 (2 h, 5 h, and 12 h after the end of the infusion) and on days 2, 8, and 15. Blood samples were collected throughout the study to analyse blood coagulation parameters, including prothrombin time, activated partial thromboplastin time, and immunogenicity. Pharmacokinetic parameters, including area under the concentration time curve ($AUC_{0\text{-}t}$), maximum concentration (C_{max}), and time to reach maximum concentration (t_{max}), were determined from the concentration–time data, where feasible, for tisotumab vedotin and free MMAE by non-compartmental analysis.

Outcomes

The primary outcome was the safety and tolerability of tisotumab vedotin, assessed by the frequency of adverse events, serious adverse events, infusion-related adverse events, CTCAE grade 3 or worse adverse events, and study drug-related adverse events. A serious adverse event was defined as any adverse event that required an extended stay in hospital, resulted in persistent or significant incapacity or dysfunction, led to a congenital anomaly or birth defect, was deemed medically important, resulted in death, or life-threatening.

Secondary outcomes were establishing the maximum tolerated dose and recommended phase 2 dose, long-term tolerability of tisotumab vedotin (including skin disorders, bleeding events, and neuropathy), pharmacokinetic profile, and antitumour activity of tisotumab vedotin. Prespecified antitumour activity endpoints included the proportion of patients who had an objective response (complete response or partial response); those who achieved disease control (complete response, partial response, or stable disease); progression-free survival, defined as the number of days from the first day of the first cycle to the first progressive disease or death; and duration of response, defined as the number of days from the first documented objective tumour response (complete or partial) to the date of first progressive disease or death.

	Dose escalation (n=27)	Dose expansion (n=147)
Age, years	63 (58–67)	59 (52–67)
Sex		
Female	18 (67%)	101 (69%)
Male	9 (33%)	46 (31%)
Race		
White	27 (100%)	136 (93%)
Black	0	2 (1%)
Asian	0	4 (3%)
Other	0	3 (2%)
Missing	0	2 (1%)
ECOG performance status		
0	13 (48%)	60 (41%)
1	13 (48%)	86 (59%)
Missing	1 (4%)	1 (1%)
Primary tumour type		
Bladder	2 (7%)	15 (10%)
Cervix	2 (7%)	34 (23%)
Endometrium	3 (11%)	14 (10%)
Oesophagus	4 (15%)	15 (10%)
NSCLC	4 (15%)	15 (10%)
Ovary	7 (26%)	36 (24%)
Prostate	4 (15%)	18 (12%)
SCCHN	1 (4%)	..
Number of previous therapies		
All	3 (2–6)	3 (2–4)
Bladder	..	2 (1–3)
Cervix	..	2 (2–3)
Endometrium	..	1·5 (1–3)
Oesophagus	..	2 (1–3)
NSCLC	..	2 (1–4)
Ovary	..	4 (3–6)
Prostate	..	4 (3–5)
SCCHN	..	..

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. SCCHN=squamous cell carcinoma of the head and neck.

Table 1: **Baseline characteristics**

Prespecified exploratory endpoints, including analyses of tissue factor expression in tumour biopsies, protein biomarker candidates, circulating concentrations of tissue factor, and circulating free DNA, are ongoing.

Statistical analysis

We report data from the completed dose-escalation phase and the ongoing expansion phase (data cutoff date Feb 1, 2018 [July 24, 2017 for the cervical cohort activity analysis]) of the InnovaTV 201 study.

The sample size of the dose-escalation phase was calculated as a maximum of 48 patients based on the 3+3 design with three to six patients in each dose cohort. The estimated sample size for the dose-expansion phase was 144 patients, which had 76% power

	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event, n (%)	65 (44%)	68 (46%)	8 (5%)	6 (4%)
Epistaxis	102 (69%)	0	0	0
Nausea	74 (50%)	3 (2%)	0	0
Fatigue	68 (46%)	14 (10%)	0	0
Alopecia	64 (44%)	0	0	0
Conjunctivitis	58 (39%)	5 (3%)	0	0
Decreased appetite	51 (35%)	2 (1%)	0	0
Constipation	50 (34%)	2 (1%)	0	0
Diarrhoea	42 (29%)	2 (1%)	0	0
Vomiting	37 (25%)	5 (3%)	0	0
Dry eye	32 (22%)	0	0	0
Neuropathy peripheral	31 (21%)	2 (1%)	0	0
Weight decreased	25 (17%)	0	0	0
Abdominal pain	24 (16%)	6 (4%)	0	0
Pruritus	22 (15%)	0	0	0
Myalgia	22 (15%)	0	0	0
Arthralgia	21 (14%)	0	0	0
Dyspnoea	21 (14%)	2 (1%)	0	0
Rash	21 (14%)	1 (1%)	0	0
Insomnia	20 (14%)	1 (1%)	0	0
Back pain	18 (12%)	1 (1%)	0	0
Cough	18 (12%)	0	0	0
Headache	17 (12%)	0	0	0
Hypokalaemia	16 (11%)	6 (4%)	0	0
AST increased	16 (11%)	1 (1%)	0	0
Peripheral sensory neuropathy	13 (9%)	3 (2%)	0	0
Pyrexia	13 (9%)	1 (1%)	0	0
ALT increased	13 (9%)	2 (1%)	0	0
Uncoded	13 (9%)	1 (1%)	0	0
Hypomagnesaemia	12 (8%)	2 (1%)	0	0
Anaemia	12 (8%)	8 (5%)	0	0
Muscular weakness	11 (7%)	1 (1%)	0	0
Urinary tract infection	10 (7%)	2 (1%)	0	0
Mucosal inflammation	10 (7%)	1 (1%)	0	0
Stomatitis	10 (7%)	1 (1%)	0	0
Upper respiratory tract infection	8 (5%)	1 (1%)	0	0
Vaginal haemorrhage	7 (5%)	2 (1%)	0	0
Blood ALP increased	7 (5%)	1 (1%)	0	0
Neutropenia	6 (4%)	3 (2%)	0	0
Ulcerative keratitis	6 (4%)	0	1 (1%)	0
Anxiety	5 (3%)	1 (1%)	0	0
Asthenia	5 (3%)	1 (1%)	0	0
Malaise	5 (3%)	1 (1%)	0	0
Dehydration	4 (3%)	2 (1%)	0	0
Hypertension	4 (3%)	2 (1%)	0	0
Blood CPK increased	4 (3%)	1 (1%)	0	0
Peripheral motor neuropathy	4 (3%)	1 (1%)	0	0
Hyponatraemia	3 (2%)	3 (2%)	2 (1%)	0
Colitis	3 (2%)	2 (1%)	0	0
GGT increased	3 (2%)	2 (1%)	0	0
Lower respiratory tract infection	3 (2%)	2 (1%)	0	0
Dysphagia	2 (1%)	2 (1%)	0	0

(Table 2 continues on next page)

	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)				
Gastroenteritis	2 (1%)	1 (1%)	0	0
Infection	2 (1%)	1 (1%)	0	0
Polyneuropathy	2 (1%)	2 (1%)	0	0
Tumour pain	2 (1%)	1 (1%)	0	0
Hyperglycaemia	1 (1%)	2 (1%)	0	0
Hypoacusis	1 (1%)	1 (1%)	0	0
Hypophosphataemia	1 (1%)	2 (1%)	0	0
Lymphocyte count decrease	1 (1%)	2 (1%)	0	0
Neutrophil count decrease	1 (1%)	1 (1%)	0	0
Pulmonary embolism	1 (1%)	1 (1%)	0	0
Hydronephrosis	0	2 (1%)	0	0
Ankle fracture	0	1 (1%)	0	0
Cellulitis	0	1 (1%)	0	0
Clostridium difficile colitis	0	1 (1%)	0	0
Corneal lesion	0	1 (1%)	0	0
Demyelinating polyneuropathy	0	1 (1%)	0	0
Device failure	0	1 (1%)	0	0
General physical health deterioration	0	1 (1%)	0	2 (1%)
Gastrointestinal haemorrhage	0	1 (1%)	0	0
Gastrointestinal ulcer haemorrhage	0	1 (1%)	0	0
Haemorrhage	0	1 (1%)	0	0
Hypoxia	0	1 (1%)	0	0
Ischaemic stroke	0	1 (1%)	0	0
Kidney infection	0	1 (1%)	0	0
Medical device site haemorrhage	0	1 (1%)	0	0
Metastases to CNS	0	1 (1%)	0	1 (1%)
Pneumonia	0	1 (1%)	0	1 (1%)
Postoperative wound infection	0	1 (1%)	0	0
Pyelonephritis	0	1 (1%)	0	0
Respiratory tract infection	0	1 (1%)	0	0
Sepsis	0	1 (1%)	1 (1%)	0
Small intestine obstruction	0	1 (1%)	0	0
Stress fracture	0	1 (1%)	0	0
Subileus	0	1 (1%)	0	0
Tumour haemorrhage	0	1 (1%)	0	0
Urethral stenosis	0	1 (1%)	0	0
Urethritis	0	1 (1%)	0	0
Urosepsis	0	1 (1%)	0	0
Febrile neutropenia	0	0	2 (1%)	0
Diabetes mellitus inadequate control	0	0	1 (1%)	0
Hyperbilirubinaemia	0	0	1 (1%)	0
Hypoglycaemia	0	0	1 (1%)	0
Neutropenic sepsis	0	0	1 (1%)	0
Oesophageal perforation	0	0	1 (1%)	0
Disease progression	0	0	0	1 (1%)
Oesophageal cancer metastatic	0	0	0	1 (1%)

Adverse events of grade 1–2 occurring in ≥10% of patients and all grade ≥3 events are shown. Medical Dictionary for Regulatory Activities preferred terms are used. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CPK=creatine phosphokinase. GGT=γ-glutamyltransferase.

Table 2: **Treatment-emergent adverse events in the dose-expansion phase**

to detect adverse events with an incidence of 1% and 95% power to detect 2% incidence. On the basis of preliminary activity data within the cervical and ovarian cohorts (cutoff June 26, 2017), the study protocol was amended on Sep 26, 2017 to allow for the expansion of these cohorts to include a maximum of about 55 and 30 patients, respectively; thus causing the study to exceed the original sample size estimates. The remaining tumour cohorts recruited about 14 patients each.

The full analysis population, which was comprised of all patients who received at least one dose of study drug, was used for the evaluation of all endpoints. Safety evaluations and pharmacokinetic parameters were summarised descriptively. For the activity analysis, investigator-assessed objective response was determined with the corresponding two-sided 95% CIs (calculated via the Clopper-Pearson method). We used the Kaplan-Meier method to estimate the median progression-free survival and duration of response, which were presented with two-sided 95% CIs. Deaths that occurred within 60 days of the last visit were included in the analysis. Further exploratory analysis of subsets of data might be performed in preparation for subsequent studies.

We used SAS (version 9.4) and R (version 3.5.1) for all statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT02001623.

Role of the funding source

The funder designed the study in collaboration with a subgroup of investigators, managed the clinical trial database, including oversight of data collection, analysis, and interpretation, and provided medical writing assistance. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 9, 2013, and May 18, 2015, 27 patients were enrolled to eight sequential dose cohorts (figure 1). Between Oct 8, 2015, and April 26, 2018, 147 patients were enrolled to the dose-expansion phase, including 15 with bladder cancer, 34 with cervical cancer, 14 with endometrial cancer, 15 with oesophageal cancer, 15 with non-small-cell lung cancer, 36 with ovarian cancer, and 18 with prostate cancer (figure 1). Patient characteristics for all patients enrolled are listed in table 1.

In the dose-escalation phase, three of 27 patients had a dose-limiting toxicity (type 2 diabetes mellitus, mucositis, and neutropenic fever), all in the 2·2 mg/kg dose cohort and all of which were grade 3. The maximum tolerated dose or recommended phase 2 dose was defined as 2·0 mg/kg. Treatment-emergent adverse events for the dose-escalation phase are listed in the appendix (p 3).

In the dose-expansion phase, the median follow-up time at data cutoff was 2·8 months (IQR 1·4–4·4). Of the

	All patients (n=147)	Bladder cancer (n=15)	Cervical cancer (n=34)	Endometrial cancer (n=14)	Oesophageal cancer (n=15)	NSCLC (n=15)	Ovarian cancer (n=36)	Prostate cancer (n=18)*
Objective response								
N (%)	23 (15·6%)	4 (26·7%)	9 (26·5%)	1 (7·1%)	2 (13·3%)	2 (13·3%)	5 (13·9%)	0
95% CI	10·2–22·5	7·8–55·1	12·9–44·4	0·2–33·9	1·7–40·5	1·7–40·5	4·7–29·5	0–0·2

Confirmed reponses are shown. Responses were assessed by investigators, as per Response Evaluation Criteria in Solid Tumors (version 1·1). Six patients in the prostate cohort did not have measurable disease at baseline; therefore, we used prostate-specific antigen concentrations to evaluate responses. The full analysis population was comprised of patients who received at least one dose of study drug. NSCLC=non-small-cell lung cancer. *Neither radiographic imaging nor prostate-specific antigen concentration showed a response in these patients.

Table 3: **Antitumour activity in the dose-expansion phase, full analysis population**

147 patients treated, 27 (18%) required one or more dose reductions. Across tumour types, the most commonly (occurring in ≥20% of patients) reported treatment-emergent adverse events of any grade were epistaxis (102 [69%] of 147 patients), fatigue (82 [56%]), nausea (77 [52%]), alopecia (64 [44%]), conjunctivitis (63 [43%]), decreased appetite (53 [36%]), constipation (52 [35%]), diarrhoea (44 [30%]), vomiting (42 [29%]), peripheral neuropathy (33 [22%]), dry eye (32 [22%]), and abdominal pain (30 [20%]; table 2). Treatment-emergent adverse events of grade 3 or worse occurred in 82 (56%) of 147 patients. The most commonly (occurring in >2% of patients) reported treatment-emergent adverse events of grade 3 or worse were fatigue (14 (10%) of 147 patients), anaemia (eight [5%]), abdominal pain (six [4%]), hypokalaemia (six [4%]), conjunctivitis (five [3%]), hyponatraemia (five [3%]), and vomiting (five [3%]). 60 (41%) of 147 patients had a treatment-emergent adverse event of at least grade 3 that was related to the study drug.

Treatment-emergent serious adverse events occurred in 67 (46%) of 147 patients. The most common treatment-emergent serious adverse events (occurring in >2% of patients) were vomiting (six [4%]), abdominal pain (five [3%]), and anaemia (four [3%]; appendix p 4). 39 (27%) of 147 patients experienced a treatment-emergent serious adverse event deemed related to study drug. Discontinuations related to adverse events occurred in 32 (22%) of 147 patients. 17 (12%) of 147 patients had an infusion-related event. The most frequent infusion-related events were abdominal pain and vomiting, both occurring in three (2%) of 147 patients.

Adverse events of special interest, as per protocol, included bleeding-related events, neuropathy, and ocular events (conjunctivitis, ulceration, keratitis, and symblepharon). Epistaxis was the most commonly reported bleeding-related adverse event, of which 98% (100 of 102) were grade 1 in severity. No grade 4–5 bleeding events were reported in the dose-expansion phase. Neuropathy of any grade occurred in 63 (43%) of 147 patients, with ten (7%) patients having neuropathy of at least grade 3 (appendix p 5). The median time to onset of neuropathy was 8·7 weeks (IQR 3·0–14·1). In patients with neuropathy, 51 (81%) of 63 patients had received prior taxane chemotherapy, the most common of which was paclitaxel. At the time of this analysis, ten (16%) of 63 patients had neuropathy events resolved, including seven patients with previous exposure to taxane. 88 (60%) of 147 patients had an ocular event (any grade). 63 (43%) of all patients experienced conjunctivitis and ocular adverse events occurred in 11 (7%) patients (appendix p 6). Implementation of ocular mitigation strategies substantially reduced the incidence of conjunctivitis, which decreased from 43 (56%) of 77 patients to 20 (29%) of 70 patients (appendix p 6).

There were three (11%) deaths among the 27 patients enrolled in the dose-escalation phase, none of which were related to study drug. Two patients in the 0·3 mg/kg dose cohort died from disease progression and one patient (with squamous cell carcinoma of the head and neck) in the 0·6 mg/kg dose cohort died from a pharyngeal tumour haemorrhage. Six (4%) adverse events with fatal outcomes occurred in the 147 patients in the dose-expansion phase: five patients due to disease progression and one of pneumonia (table 2). These events were deemed not related to study drug, except the pneumonia, which was considered possibly related.

The pharmacokinetic profile of tisotumab vedotin was assessed in the dose-escalation phase. The profiles of mean blood concentration for tisotumab vedotin and free MMAE are shown in the appendix (p 9). Increases in exposure to tisotumab vedotin and free MMAE were proportional to dose. The C_{max} of tisotumab vedotin occurred shortly after the end of infusion, whereas concentrations of free MMAE peaked 1 week after infusion. Only low concentrations of free MMAE were detected in the systemic circulation. Parameters reflecting exposure, including C_{max} and $AUC_{0\text{-}t}$, increased proportionally over the dose ranges examined (appendix p 7). When tisotumab vedotin was dosed at 2·0 mg/kg (n=3), the mean C_{max} value was 32·3 μg/mL and the mean $AUC_{0\text{-}t}$ value was 1256·4 h·μg/mL. Following single-dose administration of tisotumab vedotin at 2·0 mg/kg, the mean time-to-peak plasma concentration (t_{max}) was 1·2 h from the start of the infusion. The mean half-life for tisotumab vedotin at 2·0 mg/kg was an estimated 1·71 days (SD 0·20). Data on immunogenicity against the antibody are not yet available.

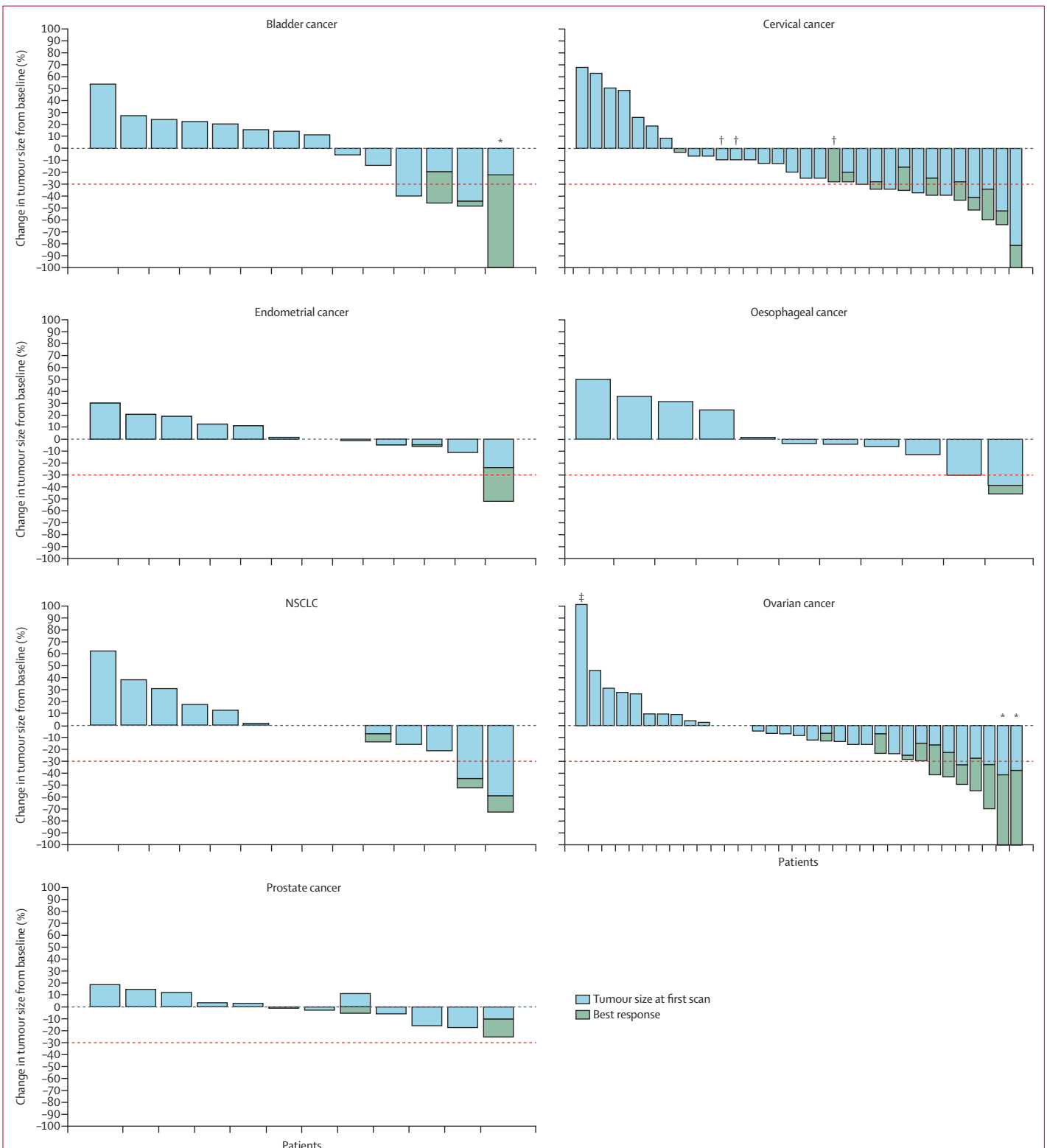

Figure 2: **Change in tumour size by cancer type**
All evaluable patients in the expansion cohorts are shown (ie, 128 patients with baseline scan data). NSCLC=non-small-cell lung cancer. *Target lesions were lymph nodes only and the sum of the target lesions post baseline was less than 10 mm. The maximum percentage change from baseline was set to +100% or −100%. †Disease progression due to new lesion. ‡Percentage change from baseline is 287·5%.

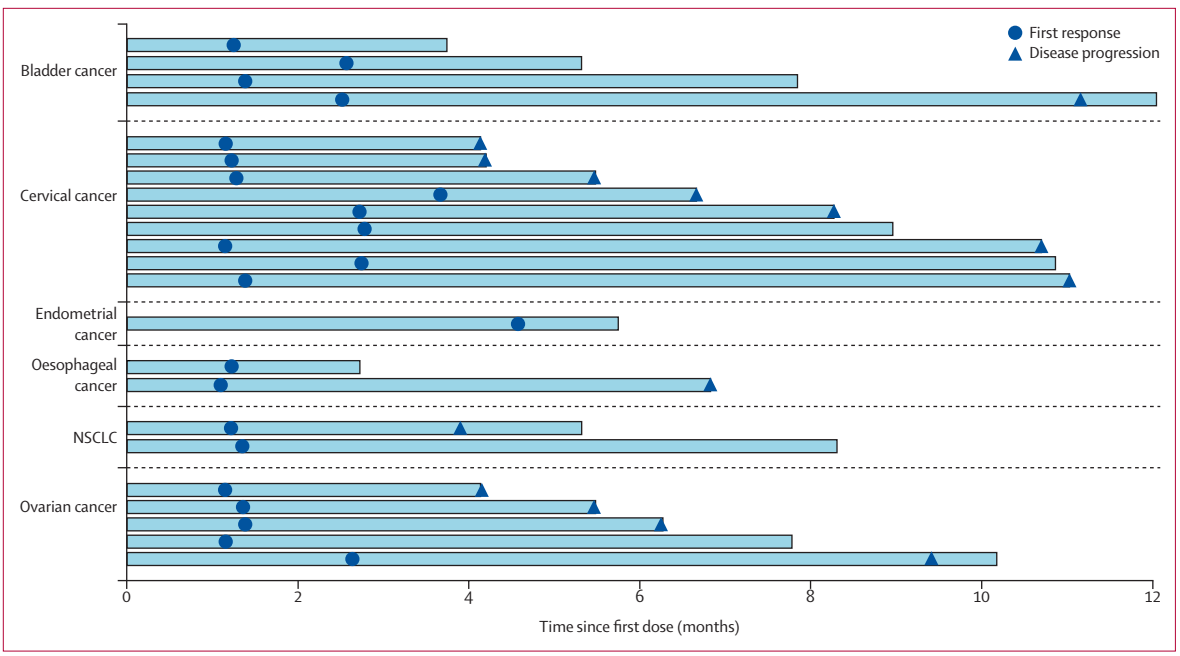

Figure 3: **Duration of response**
23 of 147 patients who achieved a confirmed response in the expansion cohorts shown. NSCLC=non-small-cell lung cancer.

Blood coagulation parameters, including prothrombin time and activated partial thromboplastin time, were not affected by treatment with tisotumab vedotin (appendix p 10). Across dose-expansion cohorts, the median prothrombin time at baseline was 10·3 s (IQR 9·9–10·7; n=134) compared with 10·4 s (10·0–10·8; n=99) at study completion. The median activated partial thromboplastin time at baseline was 30·0 s (28·3–32·4; n=134) and 30·0 s (27·1–32·6; n=99) at study completion.

In the dose-escalation phase, of the 27 patients evaluated, one patient with metastatic cervical cancer achieved a partial response at the 1·2 mg/kg dose (appendix p 8). This patient had received three previous treatment lines before the study. In the dose-expansion phase, across tumour types, 23 (15·6%, 95% CI 10·2–22·5) of 147 patients achieved a confirmed objective response (table 3). All responses were partial. In the dose-expansion cohort, change in tumour size from baseline varied among patients and across tumour types (figure 2). Among responders, the median confirmed duration of response was 5·7 months (95% CI 3·0–9·5) months (figure 3) and the median progression-free survival was 3·0 months (2·8–4·1) with 89 events (data not shown).

Discussion

This multicentre, first-in-human, phase 1–2 trial has validated the targeting of tissue factor for the treatment of advanced cancer, and has shown that tisotumab vedotin has an encouraging antitumour activity in heavily pretreated patients with multiple different tumours known to express tissue factor. The safety profile of tisotumab vedotin 2·0 mg/kg once every 3 weeks was generally consistent with other MMAE-based antibody–drug conjugates, although epistaxis and conjunctivitis seem to be more frequent with tisotumab vedotin than with previously assessed drugs of this type. Bleeding events other than epistaxis were consistent with those expected for a population of patients treated with chemotherapy, indicating that epistaxis was not a signal for a general bleeding disorder. Ocular toxicities have been reported with antibody–drug conjugates that include ravtansine and monomethyl auristatin F; however, they are rarely described for antibody–drug conjugates that use MMAE.[25] We speculate that the increased frequency of epistaxis and conjunctivitis are related to underlying inflammation or increased localised expression of tissue factor in the affected area. We used an ocular mitigation plan during the study, which reduced the frequency and severity of ocular adverse events, including conjunctivitis. Similar ocular mitigation strategies have been used prophylactically with other antibody–drug conjugates to manage ocular events.[25] Peripheral neuropathy, a known toxicity of MMAE-based antibody–drug conjugates, was seen in patients treated with tisotumab vedotin; most events were mild to moderate in severity and occurred in patients with previous exposure to taxanes.[26] In the present study, three dose-limiting toxicities were reported in the dose-escalation phase, one of which was type 2 diabetes mellitus. Hyperglycaemia has been described as a dose-limiting toxicity in other MMAE-based antibody–drug conjugates, such as brentuximab vedotin and DMOT4039A, and is probably due to the cytotoxic payload.[26,27]

The results of this trial support the use of an antibody–drug conjugate-based approach to target tissue factor,

the main initiator of the extrinsic pathway of blood coagulation.[4] Coagulation parameters, such as prothrombin time and activated partial thromboplastin time, were not affected by tisotumab vedotin administration. Furthermore, despite grade 1–2 epistaxis occurring in 69% of patients receiving tisotumab vedotin, no grade 4–5 bleeding events were seen in patients in the dose-expansion phase. These findings corroborate previous non-clinical toxicology studies of tisotumab vedotin in cynomolgus monkeys, which did not affect functional bleeding time or systemic parameters of coagulation at doses up to 5–6 mg/kg.[1]

Although this trial was not designed or powered to assess antitumour activity, we report encouraging preliminary antitumour activity for tisotumab vedotin in a broad population of patients with heavily pretreated, locally advanced or metastatic (or both) cancers of the bladder, cervix, endometrium, oesophagus, lung, and ovary. Biopsy or archived samples were collected at study entry for all patients, and our ongoing analysis will assess the correlation between tumour tissue factor expression and the antitumour activity of tisotumab vedotin to assess the value of tissue factor expression as a biomarker for treatment response.

Limitations of this phase 1–2 open-label study include a small sample size in some tumour types and the absence of overall survival as a prespecified endpoint.

In summary, our findings support further investigation of tisotumab vedotin. Several studies are underway, including InnovaTV 207 and InnovaTV 204. InnovaTV 207 (NCT03485209) is an ongoing phase 2 study evaluating the activity, safety, and tolerability of tisotumab vedotin monotherapy administered every 3 weeks in patients with relapsed, locally advanced or metastatic colorectal cancer, squamous non-small-cell lung cancer, pancreatic cancer, or squamous cell carcinoma of the head and neck. Following on from the encouraging preliminary activity seen in the cervical cancer cohort in this study, InnovaTV 204 (NCT03438396) is an ongoing phase 2 study evaluating the activity, safety, and tolerability of tisotumab vedotin monotherapy in patients with recurrent or metastatic cervical cancer that had progressed during or after treatment with standard first-line therapy.

Contributors

JSdB, UL, RAR, SG, and KW conceived, designed, and planned the study. JSdB, UL, NC, DSH, FCT, J-PM, H-TA, RP, RHJ, DN, BMS, JFS, JY, JEA, PMM-S, MDF, DC, and ED acquired the data. KW analysed the data. All authors helped to interpret the data, were involved in the development, review, or revision of the manuscript, and gave approval for submission. JSdB and UL were responsible for the final decision to submit for publication.

Declaration of interests

JSdB reports personal fees from AstraZeneca, Astellas, Genentech, Roche, GlaxoSmithKline, Merck, Genmab, Sanofi-Aventis, and Pfizer, outside the submitted work. DSH reports grants from Bayer, Lilly, Genentech, Loxo Oncology, Pfizer, Amgen, Mirati, Ignyta, Merck, Daichii-Sanko, Eisai, Adaptimmune, AbbVie, AstraZeneca, Bristol-Myers Squibb, Genmab, Infinity, Kite, Kyowa, Medimmune, Molecular Template, Novartis, and Takeda; personal fees from Mirna and Loxo Oncology; a consulting or adviser role for Bayer, Baxter, Guidepoint Global, and Janssen; an adviser role for Molecular Match; and ownership interest in Oncoresponse, outside the submitted work. FCT reports personal fees and non-financial support from Bristol-Myers Squibb and Pfizer, grants and personal fees from Novartis, personal fees from Achilles Therapeutics and Evelo Biosciences, and non-financial support from Ipsen, outside the submitted work. J-PM reports participation in advisory boards for INNATE, Merck Sharpe & Dohme, Debio, and Nanobitotix. RP reports from Genmab clinical trial costs to her institution, during the conduct of the study, and advisory board fees, outside the submitted work. PMM-S reports personal fees for advisory board participation from and spouse employment at Genmab, outside the submitted work. ED reports that, following her role as principal investigator at The Christie NHS Foundation Trust on this clinical study, she took up employment at AstraZeneca. KW is employed by Genmab A/S. SG and RAR are employed by Genmab Inc. All other authors declare no competing interests.

Data sharing

De-identified data that support the findings of this study are available on request to bona fide researchers who provide a methodologically sound proposal. Data will be made available 24 months after study completion. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

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