Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study

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Summary

Background: Few effective second-line treatments exist for women with recurrent or metastatic cervical cancer. Accordingly, we aimed to evaluate the efficacy and safety of tisotumab vedotin, a tissue factor-directed antibody–drug conjugate, in this patient population.

Methods This multicentre, open-label, single-arm, phase 2 study was done across 35 academic centres, hospitals, and community practices in Europe and the USA. The study included patients aged 18 years or older who had recurrent or metastatic squamous cell, adenocarcinoma, or adenosquamous cervical cancer; disease progression on or after doublet chemotherapy with bevacizumab (if eligible by local standards); who had received two or fewer previous systemic regimens for recurrent or metastatic disease; had measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1); and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients received 2·0 mg/kg (up to a maximum of 200 mg) tisotumab vedotin intravenously once every 3 weeks until disease progression (determined by the independent review committee) or unacceptable toxicity. The primary endpoint was confirmed objective response rate based on RECIST (version 1.1), as assessed by the independent review committee. Activity and safety analyses were done in patients who received at least one dose of the drug. This study is ongoing with recruitment completed and is registered with ClinicalTrials.gov, NCT03438396.

Findings 102 patients were enrolled between June 12, 2018, and April 11, 2019; 101 patients received at least one dose of tisotumab vedotin. Median follow-up at the time of analysis was 10·0 months (IQR 6·1–13·0). The confirmed objective response rate was 24% (95% CI 16–33), with seven (7%) complete responses and 17 (17%) partial responses. The most common treatment-related adverse events included alopecia (38 [38%] of 101 patients), epistaxis (30 [30%]), nausea (27 [27%]), conjunctivitis (26 [26%]), fatigue (26 [26%]), and dry eye (23 [23%]). Grade 3 or worse treatment-related adverse events were reported in 28 (28%) patients and included neutropenia (three [3%] patients), fatigue (two [2%]), ulcerative keratitis (two [2%]), and peripheral neuropathies (two [2%] each with sensory, motor, sensorimotor, and neuropathy peripheral). Serious treatment-related adverse events occurred in 13 (13%) patients, the most common of which included peripheral sensorimotor neuropathy (two [2%] patients) and pyrexia (two [2%]). One death due to septic shock was considered by the investigator to be related to therapy. Three deaths unrelated to treatment were reported, including one case of ileus and two unknown causes.

Interpretation Tisotumab vedotin showed clinically meaningful and durable antitumour activity with a manageable and tolerable safety profile in women with previously treated recurrent or metastatic cervical cancer. Given the poor prognosis for this patient population and the low activity of current therapies in this setting, tisotumab vedotin, if approved, would represent a new treatment for women with recurrent or metastatic cervical cancer.

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Introduction

Although advances in immunisation might prevent cervical cancer, it remains the fourth most common and fourth deadliest female cancer globally.[1] Recurrent or metastatic cervical cancer remains a substantial cause of mortality in women.[2] Platinum-based doublet chemotherapy had been the established standard of care over single-agent therapy in the first-line setting.[3–5] The addition of bevacizumab to this regimen has shown a survival benefit, leading to the current first-line standard

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for research articles, with no language restrictions, published up to Nov 5, 2020, using the search terms "tissue factor" or "thromboplastin" or "CD142" and "cervical cancer." This search found that there is no defined standard of care in the second-line or later setting for recurrent or metastatic cervical cancer and insufficient data on the efficacy of second-line treatment options if disease progression occurs during or after first-line standard of care (doublet chemotherapy with bevacizumab [if eligible by local standards]). Moreover, the search confirmed that tissue factor is highly prevalent in cervical cancer and that it is implicated in disease progression. The search also revealed that tisotumab vedotin is the first tissue factor-directed therapy under investigation for patients with cancer and that in the first-in-human, phase 1/2 innovaTV 201 study (NCT02001623), it was well tolerated with encouraging antitumour activity across a number of cancer types, including the cervical cancer cohort (n=55).

Added value of this study

To our knowledge, the innovaTV 204 study is the first large phase 2 study of an antibody–drug conjugate directed against tissue factor for the treatment of patients with previously treated recurrent or metastatic cervical cancer. Tisotumab vedotin showed durable and clinically meaningful responses in this advanced cervical cancer population. The study also showed a manageable and tolerable safety profile of tisotumab vedotin in these patients.

Implications of all the available evidence

This study shows the potential of tisotumab vedotin as a novel treatment option for recurrent or metastatic cervical cancer in the second-line or later setting, addressing an unmet need in this patient population. Further investigation of tisotumab vedotin for previously treated recurrent or metastatic cervical cancer is warranted.

of care: paclitaxel plus either platinum or topotecan with bevacizumab (in eligible patients).[6,7] However, intolerance and eventual resistance associated with these regimens limit their use and often result in disease progression.[8]

For a large proportion of patients with recurrent or metastatic cervical cancer who require treatment beyond front-line therapy, there is no established second-line standard of care, creating an important unmet need. Monotherapy with cytotoxic agents, the mainstay in the second-line setting,[9,10] have shown poor benefit–risk profiles, with low response rates (objective response rate <15%).[11–15] Additionally, very little data exist on single-agent chemotherapy after progression with current first-line standard of care with bevacizumab. On June 12, 2018, the US Food and Drug Administration (FDA) approved pembrolizumab for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (combined positive score ≥1) as determined by an FDA-approved test. Approval was granted on the basis of the KEYNOTE-158 study, in which modest (14·3% objective response; n=77) yet durable responses were reported.[10,16] Notably, the trial did not wholly reflect the current second-line population because fewer than half (42%) of patients received bevacizumab and nearly all (94%) patients had squamous histology.[16] Given the minimal effectiveness of current second-line treatment options and no second-line standard of care, alternative targets and mechanisms of action might be of value to meet the need for novel effective therapies for women with previously treated recurrent or metastatic cervical cancer.[17]

Tisotumab vedotin is an investigational antibody–drug conjugate directed against tissue factor (TF), a protein highly prevalent in multiple solid tumours, including cervical cancer.[18–21] Tisotumab vedotin binds to TF on target cells and, upon internalisation, releases monomethyl auristatin E (MMAE), a microtubule-disrupting agent, resulting in cell cycle arrest and apoptotic cell death.[22,23] The direct cytotoxicity associated with tisotumab vedotin might be augmented by bystander cytotoxicity of adjacent tumour cells and multiple immune-related effects, including immunogenic cell death, antibody-dependent cellular toxicity, and antibody-dependent cellular phagocytosis.[23,24]

In this phase 2 trial, we aimed to evaluate the activity and safety of tisotumab vedotin in women with previously treated recurrent or metastatic cervical cancer.

Methods

Study design and participants

This multicentre, open-label, single-arm, phase 2 trial enrolled patients across 35 academic centres, hospitals, and community practices in Europe and the USA. Eligible patients were aged 18 years or older and had recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology; had progressive disease during or after doublet chemotherapy (paclitaxel plus either platinum or topotecan) plus bevacizumab, if eligible; had received two or fewer previous systemic regimens for recurrent or metastatic cervical cancer (adjuvant or neoadjuvant chemotherapy, with or without radiotherapy, was not counted as a previous systemic regimen); had measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1),[25] as evaluated by the independent review committee (IRC); and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients were required to have acceptable renal and

liver function (glomerular filtration rate >50 mL/min, calculated with the Cockcroft-Gault equation; hepatic alanine aminotransferase and aspartate aminotransferase ≤3×upper limit of normal [ULN; if a primary liver malignancy was present then ≤5×ULN was allowed]; and bilirubin ≤1·5×ULN, but direct bilirubin ≤2×ULN in patients diagnosed with Gilbert's syndrome), acceptable haematological status (haemoglobin ≥5·6 mmol/L [9·0 g/dL]), absolute neutrophil count ≥1·5×10⁹ cells per L, and platelet count ≥100×10⁹ per L assessed at least 2 weeks after transfusion with blood products, growth factor support, or both), and a life expectancy of at least 3 months. Patients on anticoagulation therapy were included subject to protocol-defined criteria (appendix p 5). Patients with previous treatment with MMAE-containing drugs, radiotherapy within 21 days before first administration of study drug, known coagulation defects, ongoing major bleeding, active ocular surface disease (ie, disorders of the cornea, conjunctiva, eyelids, and lacrimal glands), a history of cicatricial conjunctivitis, Stevens-Johnson syndrome, or US National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE; version 5.0) grade 2 or worse peripheral neuropathy were excluded.

The protocol was approved by an independent ethics committee or institutional review board before initiation. The trial was done in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, Declaration of Helsinki, and all applicable regulatory requirements and according to the European Network of Gynaecological Oncological Trial Groups–Gynecologic Oncology Group model C.[26] The protocol is available in the appendix. All patients gave written informed consent.

Procedures

Patients received 2·0 mg/kg (up to a maximum of 200 mg) tisotumab vedotin intravenously every 3 weeks until IRC-verified progressive disease as per RECIST (version 1.1) or unacceptable toxicity. Dose modifications (dose interruptions and reduction from 2·0 mg/kg to 1·3 mg/kg and subsequently to 0·9 mg/kg) were permitted for the management of adverse events. Dose reductions were to be pre-approved by the sponsor's medical officer unless allowed according to protocol adverse event mitigation plans (appendix pp 6–12). Tisotumab vedotin was resumed immediately after the adverse event causing the dose interruption had improved in the opinion of the investigator. Treatment was discontinued permanently for any dose interruption of more than 12 weeks, unless approved to continue by the sponsor's medical officer. Tumour responses were assessed by the IRC and investigators using CT or MRI scans, which were done at baseline (≤28 days before cycle 1, day 1), every 6 weeks for the first 30 weeks, and every 12 weeks thereafter. Responses were confirmed by subsequent repeat imaging 4 weeks or more after the initial response assessment. All patients were followed up until death or withdrawal from the trial.

Tumours within a previously irradiated field were designated as non-target lesions unless progression was documented or a biopsy-confirmed persistence at least 90 days following completion of radiotherapy. Biopsy confirmation could be considered for either target or non-target lesions if the lesion (or lesions) measured less than 30 mm or if the treating physician determined that it was clinically indicated.

Adverse events were graded according to the CTCAE (version 5.0) and monitored throughout treatment and for 30 days after treatment ended. Treatment-emergent adverse events related to tisotumab vedotin are described in this Article. Prespecified adverse events of interest identified in the phase 1/2 study,[27] including peripheral neuropathy (a known MMAE-related adverse event), ocular, and bleeding adverse events (due to the role of TF in coagulation), were further evaluated.[28] All patients were assessed by an ophthalmologist at baseline and referred for additional evaluation in case of any ocular symptoms or abnormal ocular findings during the trial. An eye care plan to reduce the risk of and manage ocular adverse events and prespecified guidelines for dose interruptions, reductions, and discontinuation for prespecified adverse events of interest are described in the appendix (pp 4, 7–12). Laboratory values for biochemistry, haematology, and coagulation factors were assessed at screening, at every dosing visit, and at the time of treatment discontinuation.

A fresh or archival tumour biopsy was required as part of the eligibility criteria; however, determination of TF expression level was not required for enrolment. Biopsy samples were retrospectively analysed for membrane and cytoplasmic TF expression using an analytically validated immunohistochemistry assay (unpublished). A TF histology score was calculated to combine both expression and intensity of staining, as described previously.[28] Tumour cells with at least 1% TF expression were considered to be positive.

Outcomes

The primary endpoint of this study was confirmed objective response rate (defined as the proportion of complete responses and partial responses) by RECIST (version 1.1), as assessed by the IRC. Secondary efficacy endpoints included duration of response (defined as the duration between first documented objective response and first documented disease progression by the IRC or death, whichever occurred first), time to response (defined as the duration between the first dose of study drug to the first documented objective response confirmed by the IRC), and progression-free survival (defined as the duration between the first dose of study drug to the first documented disease progression by the IRC or death from any cause, whichever occurred first) assessed by the IRC; objective response rate, duration of response, time to response, and progression-free survival

	Study population (n=101)
Age, years	50 (43–58)
Race	
White	96 (95%)
Asian	2 (2%)
Black or African American	1 (1%)
Other	2 (2%)
ECOG performance status	
0	59 (58%)
1	42 (42%)
Histology	
Squamous cell carcinoma	69 (68%)
Adenocarcinoma	27 (27%)
Adenosquamous carcinoma	5 (5%)
Extrapelvic metastatic disease at baseline	95 (94%)
Recurrent disease*	
Yes	61 (60%)
No	40 (40%)
Previous cisplatin plus radiotherapy	
Yes	55 (54%)
No	46 (46%)
Previous lines of systemic therapies for recurrent or metastatic disease†	
1	71 (70%)
2	30 (30%)
Previous bevacizumab plus doublet chemotherapy‡ as first-line therapy	64 (63%)
Any previous bevacizumab	70 (69%)
Response to last systemic regimen†	
Yes	38 (38%)
No	57 (56%)
Unknown	6 (6%)
Positive TF expression§	
Membrane	77/80 (96%)
Medical history of or ongoing peripheral neuropathy	20 (20%)

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. TF=tissue factor. *First-line systemic regimen given in recurrent setting. †Systemic regimen administered in the metastatic or recurrent setting. ‡Doublet chemotherapy defined as paclitaxel–platinum or paclitaxel–topotecan. §TF-positive tumour cells were those with at least 1% expression of TF; TF expression was calculated for 80 patients who had biopsy samples.

Table 1: **Baseline demographics and clinical characteristics**

	Study population (n=101)
Objective response rate (95% CI)†	24% (16–33)
Complete response	7 (7%)
Partial response	17 (17%)
Stable disease	49 (49%)
Progressive disease	24 (24%)
Not evaluable	4 (4%)
Disease control rate (95% CI)‡	72% (63–81)
Median (95% CI) duration of response, months	8·3 (4·2–not reached)
Ongoing confirmed response ≥6 months (95% CI)	62% (37–80)
Median (IQR) time to response, months	1·4 (1·3–1·5)
Median (95% CI) progression-free survival, months	4·2 (3·0–4·4)
6-month progression-free survival rate (95% CI)	30% (21–40)
Median (95% CI) overall survival, months	12·1 (9·6–13·9)
6-month overall survival rate (95% CI)	79% (69–86)
12-month overall survival rate (95% CI)	51% (41–61)

*Independent review committee-assessed confirmed objective response rate, disease control rate, time to response, duration of response, and progression-free survival by Response Evaluation Criteria in Solid Tumors (version 1.1). †Based on the Clopper-Pearson method. ‡Disease control rate is the proportion of patients with a confirmed complete response, partial response, or stable disease.

Table 2: **Summary of response rates by independent review committee assessment***

assessed by the investigators; overall survival (defined as the duration between the first dose of study drug to death from any cause); and safety. Other secondary endpoints of immunogenicity and pharmacokinetics are not reported here. Prespecified exploratory endpoints were determination of TF expression in pretreatment tumour biopsies and assessing clinical response by TF expression level.

Statistical analysis

Study size was calculated assuming a confirmed objective response rate of 21–25% with tisotumab vedotin and the planned sample size of 100 patients provides at least 80% power to exclude an objective response rate of up to 11%, which was the previously documented observed efficacy of single-agent chemotherapy in this setting. All patients who received at least one dose of drug were included in the activity and safety analyses. We tested the objective response rate using the one-sided exact binomial test at a 2·5% α level. We calculated an exact 95% two-sided CI for the objective response rate using the Clopper-Pearson method. Patients with missing response data were counted as non-responders. IRC assessment used a two-reader plus one-reader adjudication method if readers disagreed. We estimated median (with two-sided 95% CIs) duration of response, progression-free survival, and overall survival using the Kaplan-Meier method. We summarised time to response descriptively as median with IQR. We did prespecified subgroup analyses, including histology, number of previous lines of systemic therapy, previous radiotherapy with cisplatin, previous bevacizumab in combination with doublet chemotherapy as first-line treatment, and response to most recent previous therapy, ECOG performance status, and region. Disease control rate was a post-hoc analysis, and was defined as the percentage of patients with a confirmed response (complete or partial response confirmed by subsequent repeat imaging 4 weeks or more after the initial response assessment by the IRC for the primary endpoints or the investigators for the secondary endpoints) or stable disease (as measured at least 5 weeks after the first dose

of tisotumab vedotin). Statistical analyses were done with SAS (version 9.4).

This study is registered with ClinicalTrials.gov, NCT03438396.

Role of the funding source

Genmab provided the study drug and, in partnership with Seagen, collaborated with academic investigators on study design, data collection, data analysis, data interpretation, and writing of the report. Genmab funded professional medical writers to prepare the manuscript for submission and compiled, analysed, and maintained the data. The Gynaecologic Oncology Group and European Network of Gynaecological Oncological Trial Groups had roles in study design, data collection, data interpretation, and data analysis, but not writing of the report.

Results

Of 102 patients enrolled between June 12, 2018, and April 11, 2019, 101 received at least one dose of tisotumab vedotin. One enrolled patient had a serious adverse event (spinal cord injury cauda equina) before the scheduled first dose and did not receive tisotumab vedotin (appendix p 13). Baseline characteristics of the study population are shown in table 1. Sites of disease at screening are shown in the appendix (p 17).

At data cutoff (Feb 6, 2020), median follow-up was 10·0 months (IQR 6·1–13·0) with four patients still on treatment and 33 in follow-up (appendix p 13). The median treatment duration was 4·2 months (IQR 2·5–5·5), and the median number of doses of tisotumab vedotin received was 6·0 (3·0–8·0).

The IRC-assessed confirmed objective response rate was 24% (95% CI 16–33), with seven (7%) patients achieving a complete response and 17 (17%) patients with a partial response (table 2). Median duration of response, time to response, and disease control rate (post-hoc analysis) assessed by the IRC are shown in table 2 and the appendix (p 14). Target lesions were reduced in 77 (79%) of 97 treated patients with at least one post-baseline scan (figure 1A). The durability and timing of objective responses are shown in figure 1B. Responses were generally consistent across the prespecified subgroups (figure 2).

At data cutoff, 74 progression-free survival events had occurred according to the IRC (68 progression events and six deaths). Median progression-free survival and the estimated 6-month progression-free survival rate are shown in table 2 and the appendix (p 15). Similarly, 58 deaths had accrued at data cutoff. Median overall survival and the estimated 6-month overall survival rate are shown in table 2 and figure 3. Investigator-assessed objective response rate, time to response, duration of response, and progression-free survival were similar to IRC assessment (appendix p 18).

In a prespecified exploratory analysis, an assessment of TF expression from patient tumour biopsy samples was completed for 80 (79%) of 101 patients, with 66 (83%) obtained before the last systemic therapy and 14 (18%) after the last systemic therapy. 77 (96%) of 80 patients were found to have tumours positive for membrane TF expression, as demonstrated by at least 1% of tumour cells with positive staining, with a wide range of distribution of cells staining positive for TF (median 70% [IQR 20–90]). The median TF membrane histology score for all patients at baseline was 120 (IQR 30–180).

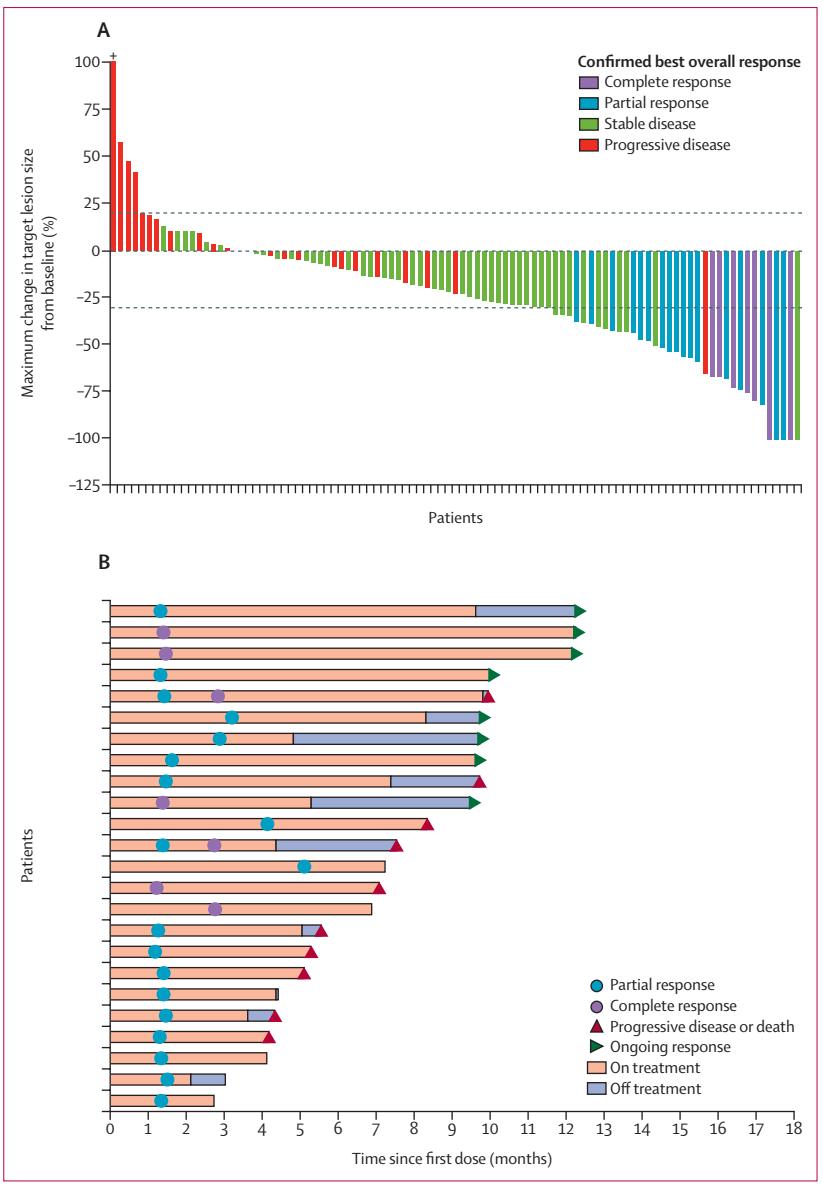

Figure 1: **Responses (per independent review committee) after tisotumab vedotin monotherapy among patients with recurrent or metastatic cervical cancer**

(A) A waterfall plot of the maximum percentage change in target lesion size in treated patients who had at least one post-baseline scan. Each bar represents a patient. Percentage changes greater than 100% were truncated at 100% (indicated by the + symbol). Dashed horizontal lines indicate 20% increase and 30% decrease in target lesion size. (B) Swimmer's plot for patients with a confirmed response. Each bar represents a patient. The circle closest to the y-axis indicates the first response. The second circle on a lane indicates a response that improved from a partial response to a complete response.

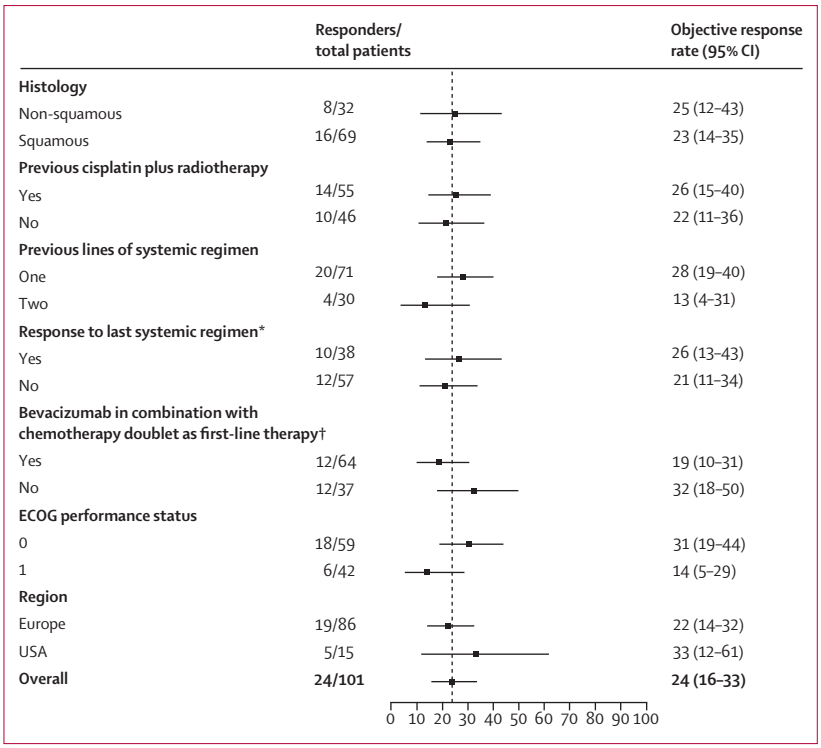

Figure 2: **Subgroup analysis of objective response rates (per independent review committee) after tisotumab vedotin monotherapy**
The dashed vertical line indicates the overall response rate of the overall study population. ECOG=Eastern Cooperative Oncology Group. *Response to last systemic regimen was not available for six patients. †The term chemotherapy doublet includes either paclitaxel plus cisplatin or carboplatin, or paclitaxel plus topotecan.

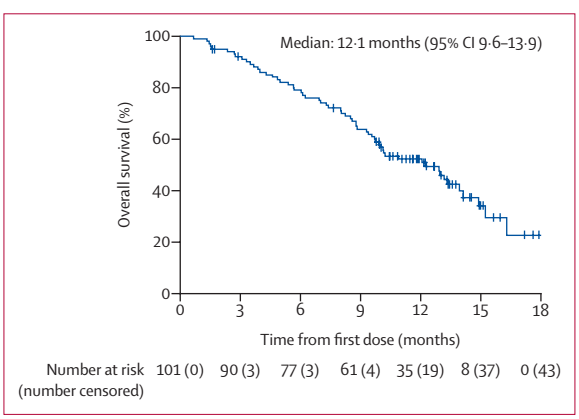

Figure 3: **Overall survival**

Of the 80 patients for whom TF expression data were available, 76 (95%) were also evaluable for response by RECIST (version 1.1). Response to tisotumab vedotin, a prespecified exploratory endpoint, was observed regardless of membrane TF expression level, and a similar distribution of TF expression was observed between the different response groups (appendix p 16).

Treatment-related adverse events occurred in 93 (92%) patients (table 3). Grade 3 or worse treatment-related adverse events were reported in 28 (28%) patients (table 3), the most common being neutropenia (three [3%] patients), fatigue (two [2%]), ulcerative keratitis (two [2%]), and peripheral neuropathies (two [2%] each with sensory, motor, sensorimotor, and neuropathy peripheral). Serious treatment-related adverse events occurred in 13 (13%) patients, the most common of which were peripheral sensorimotor neuropathy (two [2%] patients) and pyrexia (two [2%]; appendix p 19). 24 (24%) patients had a treatment-related adverse event leading to dose interruption, and 22 (22%) patients had a treatment-related adverse event leading to dose reduction; 12 (12%) patients discontinued treatment due to a treatment-related adverse event (appendix pp 20–21). One death due to septic shock was considered by the investigator to be related to therapy. Three deaths unrelated to treatment were reported, including one case of ileus and two unknown causes. Adverse events regardless of causality are described in the appendix (p 22–23).

Ocular treatment-related adverse events (by individual rather than preferred term) occurred in 54 (53%) patients, with 25 (25%) having grade 1 events, 27 (27%) having grade 2 events, and two (2%) having grade 3 events (ulcerative keratitis; table 3). The most common ocular treatment-related adverse events were conjunctivitis (26 [26%] patients), dry eye (23 [23%]), and keratitis (11 [11%]; table 3). None of the ocular treatment-related adverse events were serious. Overall, 138 ocular events occurred, of which 118 (86%) resolved based on the safety follow-up visit 30 days after the last dose. The median time to onset of the first event was 1·4 months (IQR 0·7–2·0), and the median time to resolution of each event was 0·7 months (0·3–1·6). Ocular adverse events regardless of causality are shown in the appendix (pp 24–25).

Bleeding treatment-related adverse events (by individual rather than preferred term) occurred in 39 (39%) patients, with 34 (34%) having grade 1 events, three (3%) having grade 2 events, and two (2%) having grade 3 events (rectal haemorrhage and cystitis haemorrhagic; table 3). The most common bleeding treatment-related adverse events of any grade were epistaxis (30 [30%] patients, of which 28 [28%] were grade 1), vaginal haemorrhage (seven [7%] patients), and haematuria (three [3%] patients), none of which were grade 3 or worse. Of the 57 bleeding events, 51 (90%) resolved based on the last safety follow-up visit 30 days after the last dose. The median time to onset of the first event was 0·3 months (IQR 0·2–1·1), and the median time to resolution of each bleeding event was 0·5 months (0·1–1·4). Bleeding adverse events regardless of causality are shown in the appendix (p 26). There were no clinically meaningful changes in prothrombin time, international normalised ratio, or activated partial thromboplastin time observed (data not shown).

Peripheral neuropathy treatment-related adverse events (by individual rather than preferred term) occurred in 33 (33%) patients, with 17 (17%) having grade 1 events,

nine (9%) having grade 2 events, and seven (7%) having grade 3 events. The most common treatment-related adverse events in this class were neuropathy peripheral (ten [10%] patients; two [2%] with grade 3), peripheral sensory neuropathy (nine [9%]; two [2%] with grade 3), and peripheral sensorimotor neuropathy (five [5%]; two [2%] with grade 3; table 3). Overall, 47 peripheral neuropathy events occurred in 33 patients, of which ten (21%) resolved based on safety follow-up visit 30 days after the last dose. The median onset time of the first event was 3·1 months (IQR 1·8–4·4), and the median time to resolution of each peripheral neuropathy event was 0·6 months (0·5–1·2). Peripheral neuropathy adverse events regardless of causality are shown in the appendix (p 27).

	Grade 1–2	Grade 3	Grade 4	Grade 5
Patients with at least one treatment-related adverse event	65 (65%)	25 (25%)	2 (2%)	1 (1%)
Treatment-related adverse events, by preferred terms, with an incidence of 10% or higher, or any grade 3 or worse event				
Alopecia	38 (38%)	0	0	0
Epistaxis	30 (30%)	0	0	0
Nausea	27 (27%)	0	0	0
Conjunctivitis	26 (26%)	0	0	0
Fatigue	24 (24%)	2 (2%)	0	0
Dry eye	23 (23%)	0	0	0
Myalgia	15 (15%)	0	0	0
Anaemia	12 (12%)	1 (1%)	0	0
Asthenia	12 (12%)	1 (1%)	0	0
Arthralgia	12 (12%)	0	0	0
Decreased appetite	11 (11%)	0	0	0
Keratitis	11 (11%)	0	0	0
Pruritus	10 (10%)	1 (1%)	0	0
Neuropathy peripheral	8 (8%)	2 (2%)	0	0
Constipation	8 (8%)	1 (1%)	0	0
Peripheral sensory neuropathy	7 (7%)	2 (2%)	0	0
Peripheral sensorimotor neuropathy	3 (3%)	2 (2%)	0	0
Neutropenia	1 (1%)	3 (3%)	0	0
Hypomagnesaemia	2 (2%)	0	1 (1%)	0
Peripheral motor neuropathy	1 (1%)	2 (2%)	0	0
Dehydration	1 (1%)	1 (1%)	0	0
Hypertension	1 (1%)	1 (1%)	0	0
Hypokalaemia	1 (1%)	1 (1%)	0	0
Rectal haemorrhage	1 (1%)	1 (1%)	0	0
Stomatitis	1 (1%)	1 (1%)	0	0
Ulcerative keratitis	0	2 (2%)	0	0
Colitis	0	1 (1%)	0	0
Creatinine renal clearance decreased	0	1 (1%)	0	0
Cystitis haemorrhagic	0	1 (1%)	0	0
Hypocalcaemia	0	1 (1%)	0	0
Infection	0	1 (1%)	0	0
Infusion site extravasation	0	1 (1%)	0	0
Lymphocyte count decreased	0	1 (1%)	0	0
Neutropenic sepsis	0	0	1 (1%)	0
Platelet count decreased	0	0	1 (1%)	0
Pneumonia	0	1 (1%)	0	0
Pulmonary embolism	0	1 (1%)	0	0
Septic shock	0	0	0	1 (1%)

Table 3: **Most common treatment-related adverse events in the study population (n=101)**

Discussion

Women with recurrent or metastatic cervical cancer have a high unmet clinical need because this disease is incurable and lacks a standard of care after progression on first-line treatment. Results from this pivotal phase 2 study showed that tisotumab vedotin has compelling and durable antitumour activity, with an objective response rate of 24% (including seven complete responses and 17 partial responses) and a median duration of response of 8·3 months. These clinically meaningful findings are further supported by encouraging median progression-free survival (4·2 months) and overall survival (12·1 months). The multiple mechanisms of action of tisotumab vedotin, including MMAE-directed cytotoxicity, bystander effect, and immunogenic effects, might contribute to the promising efficacy observed in our study.[24]

Disease control is a key consideration in this setting because many patients are considered to have chemotherapy-resistant tumours after first-line treatment and might have rapid disease progression. Most tumour responses with tisotumab vedotin were rapid, with a median time to response of 1·4 months, indicating potential antitumour activity within the first two treatment cycles. Furthermore, most of the treated patients (79%) with a post-baseline scan had reductions in target lesion size from baseline. Taken together with a disease control rate of 72%, these data emphasise clinical improvement in a patient population in which rapid response and reduction in tumour burden are crucial for controlling rapidly progressing disease.

Cross-trial comparisons are difficult because of differences in study designs and patient populations, but it is important to contextualise our findings relative to therapies historically used or recently approved or evaluated for treatment of recurrent or metastatic cervical cancer. Additionally, because of the potential effect that first-line treatments might have on outcomes with second-line therapies, it is difficult to compare results from trials done before the emergence of bevacizumab in the first-line recurrent or metastatic cervical cancer setting with those that have come after the emergence of bevacizumab. Before the adoption of doublet chemotherapy with bevacizumab as the first-line standard of care, objective response rates for available second-line chemotherapy agents ranged between 5% and 15%.[11–15] The objective response rate (24%), and in particular the complete responses (7%), observed in this study population, in which most patients received previous bevacizumab (if eligible), was greater than that observed with most available second-line therapies. Furthermore,

the objective response rate of 24% in this study was higher than the 11% previously reported with single-agent chemotherapy in this setting (unpublished). The lower bound of the 95% CI for the confirmed objective response rate in our study (16%) is higher than those reported for other therapies in this setting (eg, 15% for pemetrexed,[14] 14% for vinorelbine,[29] 5% for gemcitabine,[30] and 11% for bevacizumab[11]), including pembrolizumab (14·3%).[16]

A phase 2 trial done in China (the CLAP trial) evaluating combination treatment with the PD-1 inhibitor camrelizumab and the VEGFR2 inhibitor apatinib reported an investigator-assessed objective response rate (per RECIST [version 1.1]) of 55·6% (95% CI 40·0–70·4) in patients with metastatic, recurrent, or persistent cervical cancer.[31] Treatment-related grade 3 or 4 adverse events occurred in 32 (71·1%) of 45 patients, the most common of which were hypertension (11 [24·4%] of 45), anaemia (nine [20·0%]), and fatigue (seven [15·6%]). The most common potential immune-related adverse events included grade 1–2 hypothyroidism (ten [22·2%] patients) and reactive cutaneous capillary endothelial proliferation (four [8·9%]). Notably, most (30 [67%] of 45) patients had PD-L1-positive disease and a favourable prognostic for response to checkpoint therapy, only 22% had received previous bevacizumab (unreported whether any responders had received previous bevacizumab), and the objective response rate and progression-free survival were significantly lower in patients with adenosquamous histology than in patients with squamous cell carcinoma. Moreover, the study population was not reflective of an international population.

The 8·3-month median duration of response with tisotumab vedotin compares favourably with limited available data for single-agent chemotherapy drugs, which present historical median response durations of 2 months to 6 months.[32] Notably, results from these single-agent second-line chemotherapy trials do not reflect the current treatment paradigm (bevacizumab with doublet chemotherapy in the first-line setting) because they also do not consider the potential effect of first-line doublet chemotherapy plus bevacizumab on second-line outcomes. Moreover, these trials generally had small sample sizes and included both confirmed and unconfirmed response rates in the calculation of objective response rate. These historical efficacy data for second-line (and beyond) chemotherapy agents highlight the need for improved treatment options in this setting.

To our knowledge, our study is the first to address the major unmet need of women with cervical cancer whose tumours have progressed during or after doublet chemotherapy plus bevacizumab (if eligible), with 63% of the patients receiving bevacizumab together with doublet chemotherapy (paclitaxel plus platinum or topotecan) in the first-line setting and 69% receiving bevacizumab as part of their first-line, second-line, or both first and second-line treatment. The objective response rate (12 [19%] of 64 patients) observed in those who received bevacizumab with doublet chemotherapy in the first-line setting is similar to that of the overall population and shows that response might not have been substantially affected by previous exposure to bevacizumab. In the KEYNOTE-158 study,[16] only two responses were observed in the 41 patients who had received previous bevacizumab. In our study, patients with traditionally difficult-to-treat histological subtypes (adenocarcinoma and adenosquamous carcinoma) who are often under-represented in clinical trials were included, and similar response rates to the overall population were observed. The objective response rate in patients with non-squamous histology was 25%, and patients with adenocarcinoma, which is associated with poor prognosis and a high propensity for distant recurrence, represented approximately a quarter of the patient population of this study.

No clear association between the levels of membrane TF expression and confirmed best overall response was identified in this study. However, most evaluable biopsy samples (96%) in the study showed membrane TF expression (≥1%), albeit with varying levels. Therefore, it seems plausible that TF expression might be contributing to responses, and binding of tisotumab vedotin to the TF-expressing tumour cells might be sufficient to initiate tumour cell killing and induce further antitumour activity through the multiple mechanisms of action of tisotumab vedotin, including bystander killing and immunogenic effects.[23,24] Furthermore, it is important to note that TF expression in tumours is heterogeneous (both within and across tumours), that tumour TF expression levels might change over time,[20,21] and that most (83%) biopsy samples were taken before the last systemic therapy, which might also affect understanding of the association between response and level of TF expression in the tumour.

Most adverse events associated with tisotumab vedotin were mild to moderate in severity, and no new safety signals were reported. Ocular adverse events were observed in the first-in-human trial of tisotumab vedotin; thus, an eye care plan was implemented for this study.[27,28] Protocol-defined eye care measures for preventing and managing these events have evolved as experience with tisotumab vedotin grows. Although 53% of patients had an ocular treatment-related adverse event, these were predominantly grade 1 or 2 (52 of 54), with only two patients having grade 3 ocular treatment-related adverse event (both ulcerative keratitis). Most ocular adverse events were confined to the surface (conjunctival and corneal disorders) and most resolved.

The ability of tisotumab vedotin to bind to TF, the primary initiator of blood coagulation after vascular injury, prompted bleeding to be a prespecified adverse event of interest in our study. Although 39% of patients had bleeding treatment-related adverse events, most were grade 1 (34 of 39), with the most common being epistaxis (30%; grade 1, 28%). Bleeding events associated

with underlying conditions (vaginal haemorrhage and haematuria), which are often attributed to local tumour growth or previous pelvic radiotherapy, were also observed. Most bleeding treatment-related adverse events resolved. Furthermore, no clinically meaningful changes in prothrombin time, international normalised ratio, or activated partial thromboplastin time were observed which is consistent with findings from our first-in-human study, innovaTV 201.[27]

Peripheral neuropathy is a known toxicity associated with MMAE-containing antibody–drug conjugates.[33,34] Most of these treatment-related adverse events were grade 1 or 2 (in 26 of 33 of patients) and manageable. The median time to onset was 3·1 months, which is consistent with other MMAE-containing antibody–drug conjugates, with a resolution of 21%, which was limited by the protocol-defined follow-up period for this adverse event of only 30 days. Moreover, peripheral neuropathy is a common occurrence in patients with recurrent or metastatic cervical cancer previously treated with platinum and taxanes;[7] in our study, at baseline, 20 patients had a medical history of or ongoing peripheral neuropathy. This finding is consistent with data from our first-in-human study, innovaTV 201,[27] and aligned with the population being relatively young, without many comorbidities (eg, diabetes), and having received between one and two previous systemic lines.

Overall, tisotumab vedotin had a manageable safety profile. Lower rates of peripheral neuropathy, and ocular and bleeding events, compared with the first-in-human study might potentially be reflective of well-defined and stringent dose modification and preventive protocols implemented in this study.[28]

Limitations of this open-label phase 2 study include the fact that it only had one treatment group, making it difficult to fully assess effect of therapy on patient survival and possibly limiting inferences as compared with studies with a control group. Moreover, comparisons with historical studies assessing chemotherapy are limited by the differences in the study populations, especially because the historical comparator studies did not enrol patients who received the current first-line standard of care with bevacizumab and also due to differences in study conduct and procedures (eg, use of RECIST criteria and confirmation of objective response).

Tisotumab vedotin is currently being investigated as a monotherapy in other solid tumours: ovarian (NCT03657043), lung, colorectal, pancreatic, and head and neck cancers (NCT03485209). Tisotumab vedotin is also being tested in recurrent or metastatic cervical cancer in combination with a PD-1 inhibitor or platinum-based or targeted therapies (NCT03786081). These trials are evaluating tisotumab vedotin administered either every 3 weeks or on days 1, 8, and 15 of a 28-day cycle. A phase 3 randomised, open-label study evaluating tisotumab vedotin versus investigator's choice chemotherapy (NCT04697628) in recurrent or metastatic cervical cancer, with overall survival as the primary endpoint, is also currently underway.

Tisotumab vedotin is the first TF-directed antibody–drug conjugate under investigation and, if approved, would represent a new treatment modality for recurrent or metastatic cervical cancer. Data from our study, consistent with the phase 1/2 study,[28] indicate that tisotumab vedotin has a favourable benefit-to-risk profile. Given the low activity of current therapies and the poor prognosis of women with recurrent or metastatic cervical cancer, these results suggest tisotumab vedotin has the potential to change the treatment landscape for this disease, regardless of TF expression, histology, or previous treatment with doublet chemotherapy plus bevacizumab.

Contributors

All authors collected data or provided clinical and scientific input on the study design and protocol. All authors had full access to the data output and helped to interpret the data. MC, MSLT, and AL did the statistical analyses. All authors were involved in the development, review, or revision of the manuscript, and gave approval for final submission. All authors confirm the accuracy of the data and adherence of the trial to the protocol. All authors had full access to the data in the study upon request. RLC and IV were responsible for the final decision to submit for publication. AL and MC verified the data.

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Data sharing

The de-identified data that support the findings of this study are available on request to bona fide researchers who provide a methodologically sound proposal. The 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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