A phase lla study of tisotumab vedotin in patients with previously treated recurrent or metastatic cervical cancer: updated analysis of full cervical expansion cohort

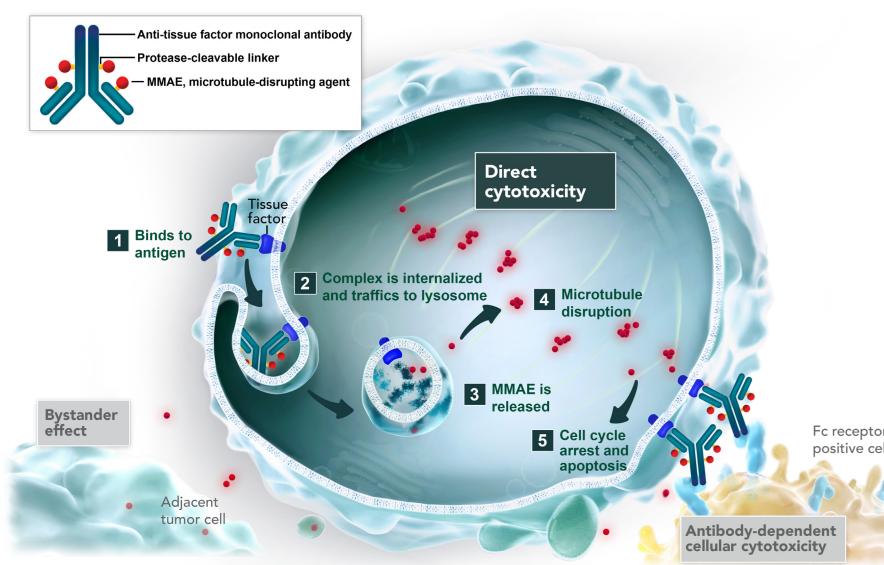
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BACKGROUND

- Recurrent or metastatic cervical cancer has a poor prognosis and current treatment options in second- or later-lines are associated with limited response rates.¹⁻³ Thus, there is a high unmet need for patients who progress after first-line therapy
- Limited data exist regarding the efficacy of current second-line therapies after first-line treatment with GOG 240 regimen (doublet chemotherapy + bevacizumab)^{4,5}
- Tissue factor (TF) is aberrantly expressed in a broad range of solid tumours, including cervical cancer,^{6,7} and TF expression has been associated with higher tumour stage and grade, higher metastatic burden and poor prognosis⁶
- Aberrant TF expression in cervical cancer makes TF a novel target for patients with cervical cancer Tisotumab vedotin (TV) is a first-in-class antibody-drug conjugate (ADC) that is designed to selectively target TF to deliver a clinically validated cytotoxic payload (monomethyl auristatin E [MMAE]) to target-expressing cells allowing for direct cytotoxicity and bystander killing, as well as antibodydependent cellular cytotoxicity^{8,9} (**Figure 1**)

Figure 1. Proposed Mechanism of Action of Tisotumab Vedotin^{8,9}



- innovaTV 201 is a phase I/IIa dose-escalation and expansion study evaluating safety, tolerability, and antitumour activity of TV in patients with previously treated locally advanced or metastatic solid tumours (NCT02001623)
- In the dose-escalation phase of the trial, TV 2.0 mg/kg every 3 weeks was the recommended phase II dose¹⁰
- The expansion phase included 7 disease-specific expansion cohorts (cervical, ovarian, endometrial, prostate, bladder, oesophageal, and non-small-cell lung cancer)
- A manageable safety profile and encouraging preliminary activity was demonstrated in the cervical cancer cohort (n=34), with a combined unconfirmed + confirmed objective response rate (ORR) of 32% by investigator assessment¹¹ and 41% as assessed by an independent review committee
- Updated results for the full cervical cancer cohort (N=55) as of 30 August 2018 are presented

OBJECTIVE

• Evaluate the safety, tolerability, and antitumour activity of TV in patients with previously treated recurrent or metastatic cervical cancer

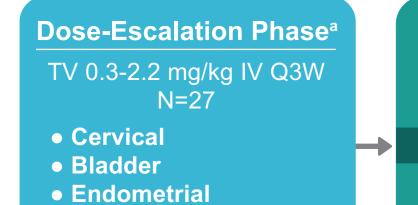
METHODS

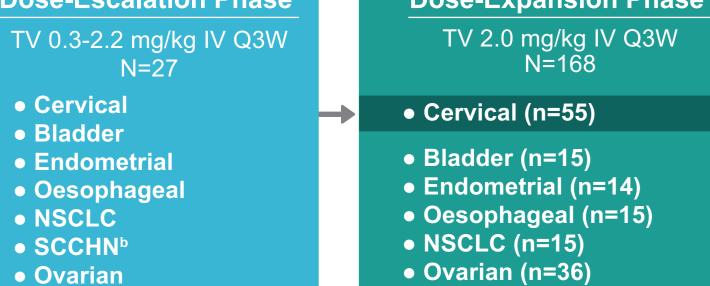
Study Design

Prostate

- innovaTV 201 is a first-in-human, open-label, single-arm, phase I/IIa dose-escalating (3+3 design) and expansion study of TV in patients with locally advanced or metastatic solid tumours known to express TF (Figure 2)
- Patients with clinical benefit (stable disease [SD] or better) at the end of 4 cycles had the option to continue TV for up to 8 additional cycles (12 cycles total) or until disease progression or unacceptable toxicity. After 12 cycles, patients with clinical benefit could continue in an extension study (NCT03245736)

Figure 2. innovaTV 201 Study Design





Dose-Expansion Phase

- Ovarian (n=36)
- Cervical Cohort (N=55) **Primary Endpoint:**

- Safety and Tolerability^d Selected Secondary Endpoi Investigator-assessed ORR by RECIST v1.1e
- Prostate (n=18)

- IV. intravenous: NSCLC, non-small-cell lung cancer: Q3W, every 3 weeks: RECIST, Response Evaluation Criteria In Solid Tumours: SCCHN, ^aTwo patients were missing race information. ^bPatients did not receive standard-of-care therapy in the first-line setting because they were refractory to treatment administered for early stage disease (concurrent chemoradiation therapy or neoadjuvant therapy). GOG 240 regimen defined as bevacizumab + doublet chemotherapy (cisplatin + paclitaxel or topotecan + paclitaxel).
- squamous cell carcinoma of the head and neck; TV, tisotumab vedotin. Subjects were enrolled into cohorts at increasing dose levels of TV in 21-day treatment cycles. The SCCHN cohort was closed by a protocol amendment due to an event of pharyngeal tumour haemorrhage with fatal outcome. The event was deemed to be most likely related to the disease itself. In phase II, ovarian and cervical cohorts were expanded to include more patients based on preliminary efficacy observed in the first 14 patients enrolled. dAE severity graded per Common Terminology Criteria for Adverse Events [CTCAE] v4.0. Computed tomography or magnetic resonance imaging was performed at baseline and every 6 weeks during the study for tumour assessments.

Patient Eligibility

- Key eligibility criteria for cervical cancer cohort:
- Recurrent or metastatic cervical cancer
- Measurable disease per Response Evaluation Criteria In Solid Tumours (RECIST) v1.1
- Progression on or following a platinum-based regimen for recurrent or metastatic cervical cancer Received ≤4 prior treatment regimens for advanced disease
- No past or current coagulation defects leading to an increased risk of bleeding

Study Objectives and Assessments

- Primary objectives: safety and tolerability
- Selected secondary objectives: antitumour activity (ORR, DCR, DOR, and PFS)
- Confirmed responses were defined with repeat imaging ≥4 weeks after initial response DCR was defined as the proportion of patients with response plus SD
- Adverse events of special interest (AESIs) were neuropathy, bleeding-related events, and ocular events
- Risk mitigation measures for ocular AEs (conjunctivitis, conjunctival ulceration, and keratitis) were used and involved use of a prophylactic steroid, lubricating eye drops, cooling eye masks worn during treatment infusion, and stricter dose modification guidance
- The efficacy-evaluable population (n=51) excluded 4 patients who were refractory to prior treatment for early stage disease but did not receive standard of care (doublet chemotherapy ± bevacizumab) for first-line treatment of recurrent or metastatic disease

RESULTS

Patients

 Among the 55 female patients enrolled in the cervical cohort, the median age was 46 years, the majority had Eastern Cooperative Oncology Group (ECOG) performance status of 1 (73%), and the most frequent histology was squamous cell carcinoma (51%) (Table 1)

N=55

- Most patients were heavily pretreated, with 28 patients (51%) having received ≥2 prior systemic therapies; 67% of patients had previously received the GOG 240 regimen (**Table 1**)
- The median duration of follow-up was 3.5 months (range, 0.6–11.8 months)
- Study dispositions are shown in Table 2

Table 1. Baseline Patient Characteristics in the Cervical Cancer Cohort

Age, median (range), years	46 (21–73)
Race, n (%) ^a	
White	49 (92)
Asian	3 (6)
Black or African American	1 (2)
ECOG performance status, n (%)	
0	15 (27)
1	40 (73)
Histology, n (%)	
Squamous	28 (51)
Adenocarcinoma	19 (35)
Adenosquamous	6 (11)
Other	2 (4)
Previous lines of systemic treatment, n (%)	
Op	4 (7)
1	23 (42)
2	17 (31)
3	6 (11)
4	5 (9)
Prior systemic therapies, n (%)	
Taxane	50 (91)
Bevacizumab	40 (73)
GOG 240 regimen ^c	37 (67)

Table 2. Study Disposition

	N=55
Treatment ongoing, n (%)	4 (7)
Withdrawn from study, n (%)	51 (93)
Due to adverse event	8 (15)
Due to progressive disease	35 (64)
Lost to follow-up	1 (2)
Othera	7 (13)

- The median duration of treatment with TV was 2.4 months (range, 0.03–10.7 months); the median number of cycles received was 4 (range, 1–14)
- Treatment-emergent AEs (TEAEs) of any grade were reported in 55 patients (100%), irrespective of causality, and grade ≥3 TEAEs were reported in 31 patients (56%) (**Table 3**)
- The most common serious AEs (≥5%) were vomiting (7%) and constipation (5%)
- The most common TEAEs are listed in Table 4
- There were no treatment-related deaths

Table 3. Safety Summary

ncidence, n (%)	N=55
II-cause TEAEs	55 (100)
Grade ≥3	31 (56)
erious AEs	29 (53)
atients with AE leading to treatment discontinuation	14 (25)
atients with AE leading to dose reduction	7 (13)

- There were no Grade ≥4 AESIs (Table 4)
- The most common neuropathy AESI was peripheral neuropathy (any grade, 35%; grade 3, 5%) - The most common bleeding-related AESIs were epistaxis (51%), vaginal haemorrhage (13%), and

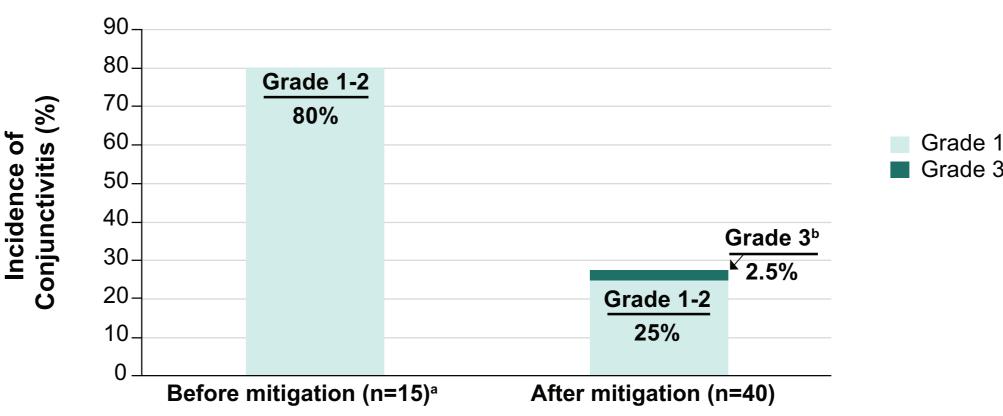
N=55

- Conjunctivitis (42%) and dry eye (22%) were the most common ocular AESIs
- The rates of conjunctivitis were reduced after implementation of mitigation measures (Figure 3)

Table 4. Most Common TEAEs and Incidence of AESIs

TEAEs in ≥20% of patients, n (%)	Any grade	Grade ≥3	
Epistaxis	28 (51)	0	
Fatigue	28 (51)	5 (9)	
Nausea	27 (49)	3 (5)	
Conjunctivitis	23 (42)	1 (2)	
Alopecia	22 (40)	0	
Decreased appetite	21 (38)	0	
Constipation	20 (36)	1 (2)	
Peripheral neuropathy	19 (35)	3 (5)	
Vomiting	19 (35)	4 (7)	
Diarrhea	16 (29)	1 (2)	
Abdominal pain	15 (27)	3 (5)	
Anaemia	13 (24)	6 (11)	
Dry eye	12 (22)	12 (22) 0	
Urinary tract infection	11 (20)	11 (20) 1 (2)	
Hypokalaemia	11 (20)	3 (5)	
Pyrexia	11 (20)	1 (2)	
Pruritus	11 (20)	0	
AESIs, n (%)	Any grade	Grade 3	
Neuropathy AESIs	29 (53)	6 (11)	
Bleeding-related AESIs	40 (73)	3 (5)	
Any ocular AESIs	34 (62)	1 (2)	

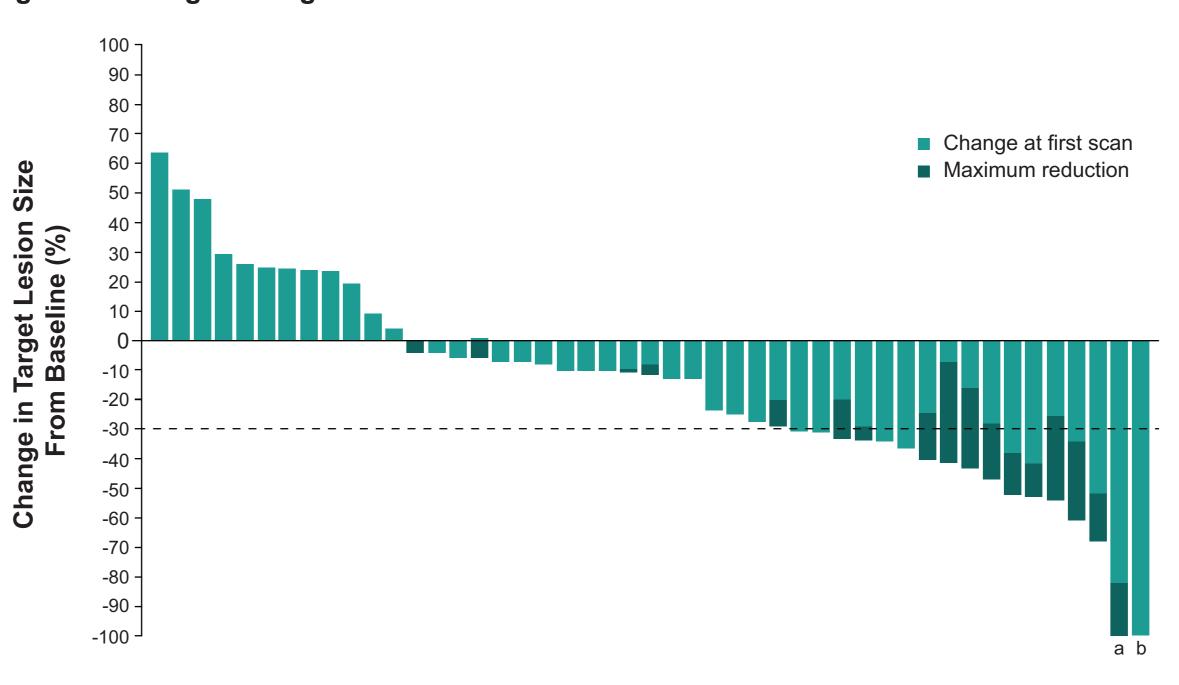
Figure 3. Incidence of Conjunctivitis Before and After Mitigation Measures



Antitumour Activity

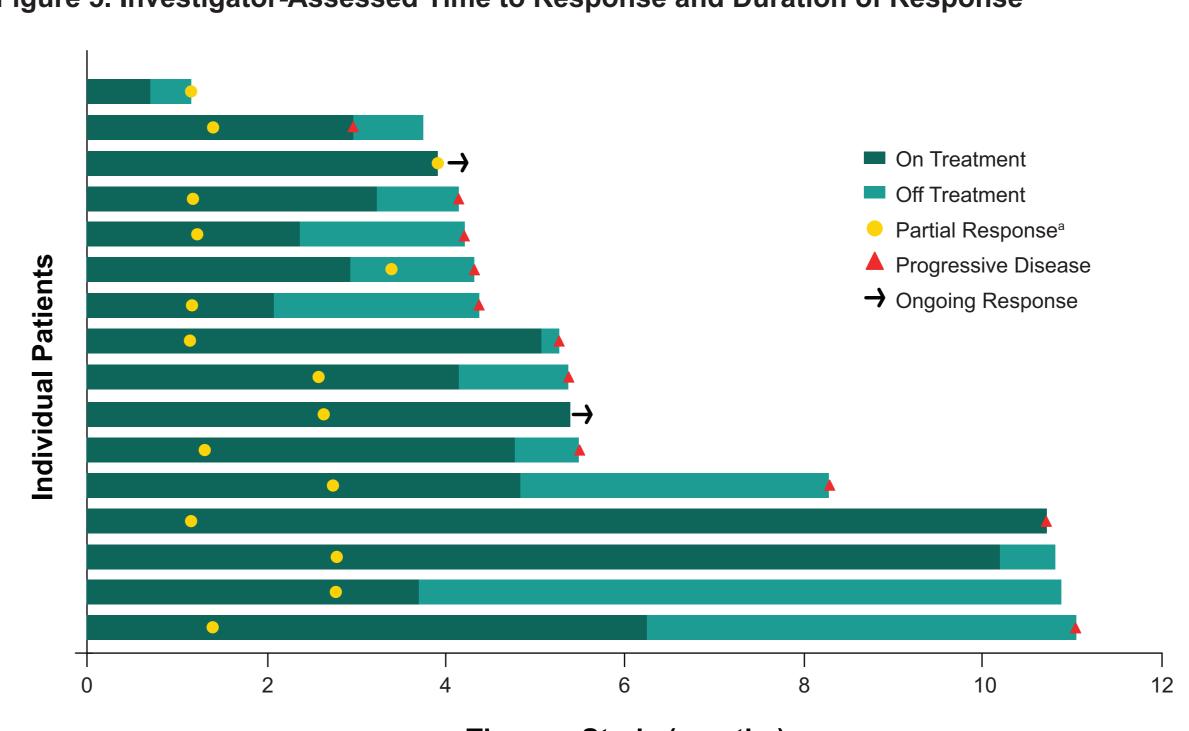
- The combined unconfirmed + confirmed ORR was 31% (95% CI: 19%–46%) (Table 5) - Eleven patients had confirmed partial response (PR), and 5 patients had unconfirmed PR, with
- 1 patient pending confirmation at the time of data cutoff
- The DCR was 63% (95% CI: 48%–76%); 31% of patients had best response of SD
- Changes in target lesion size from baseline are shown in Figure 4 Time to and duration of responses are shown in Figure 5
- The median time to response was 1.4 months (range, 1.1–3.9 months)
- The median DOR was 4.9 months (95% CI: 2.8–9.7 months)
- Four patients with confirmed PR experienced a response for >8 months The median PFS was 4.1 months (95% CI: 2.1–5.3 months)

Figure 4. Change in Target Lesion Size From Baseline



Four patients did not have post-baseline scans and were excluded from this analysis. ^aPatient had lymph node disease and persistent non-target lesions for best response of PR. ^bPatient had lymph node disease, persistent non-target lesions, and a new lesion for best response of progressive disease.

Figure 5. Investigator-Assessed Time to Response and Duration of Response



Time on Study (months)

^aResponse defined as unconfirmed + confirmed.

Responses were observed across baseline characteristic subgroups, including histological type, prior lines of therapy, and prior treatments received (**Table 5**)

Table 5. Investigator-Assessed Response per RECIST v1.1

	n	ORR, n (%) ^a	ORR 95% CI, %			
All efficacy-evaluable patients	51	16 (31)	19–46			
Histology						
Squamous	27	9 (33)	17–54			
Adenocarcinoma	18	4 (22)	6–48			
Adenosquamous	4	2 (50)	7–93			
Other	2	1 (50)	1–99			
Prior lines of systemic therapy						
1	23	8 (35)	16–57			
2	17	6 (35)	14–62			
3-4	11	2 (18)	2–52			
Prior taxane						
Yes	48	15 (31)	19–46			
No	3	1 (33)	1–91			
Prior bevacizumab						
Yes	40	12 (30)	17–47			
No	11	4 (36)	11–69			
Prior GOG 240 regimen ^b						
Yes	37	12 (32)	18–50			
No	14	4 (29)	8–58			
Combined unconfirmed + confirmed ORR. bGOG 240 regimen defined as bevacizumab + doublet chemotherapy (cisplatin + paclitaxel or topotecan +						

CONCLUSIONS

- TV demonstrated a manageable safety profile and encouraging antitumour activity in patients with
- previously treated recurrent or metastatic cervical cancer The safety profile of TV in this heavily pretreated cervical cancer cohort was acceptable and
- TV demonstrated encouraging preliminary activity in patients with recurrent or metastatic cervical
- cancer, with a 31% response rate and notable duration of response Responses were observed across histological types and irrespective of prior lines of therapy or
- type of prior therapy received
- These results support the further clinical development of TV in patients with recurrent or metastatic cervical cancer who have progressed on previous treatment
- The ongoing phase II innovaTV 204 study (NCT03438396) is investigating the antitumour activity of TV in approximately 100 patients with recurrent or metastatic cervical cancer who have had disease progression on standard-of-care first-line therapy

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