Tisotumab Vedotin in Previously Treated Recurrent/Metastatic Cervical Cancer

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Abstract (250/250 words)

Background: Advanced recurrent/metastatic cervical cancer has a 5-year survival of only 17% and no current second-line standard-of-care, representing a significant unmet need. Tissue factor (TF) is a potential therapeutic target in cervical cancer as it is frequently highly expressed and associated with poor prognosis. Tisotumab vedotin, a first-in-class antibody-drug conjugate targeting TF, has successfully demonstrated encouraging activity in solid tumors. Here we report data from the cervical cancer cohort of innovaTV 201.

Methods: Patients with recurrent/metastatic cervical cancer received tisotumab vedotin 2.0 mg/kg every 3 weeks until progressive disease, unacceptable toxicity, or consent withdrawal. Study objectives included safety and antitumor activity.

Results: Of the 55 patients, 51% had received ≥2 prior lines of treatment in the recurrent/metastatic setting; 67% prior bevacizumab+doublet chemotherapy. 51% had squamous cell carcinoma. The most common grade 3/4 treatment-emergent adverse events (AEs) were anemia (11%), fatigue (9%), and vomiting (7%). No grade 5 treatment-related AEs occurred. Investigator-assessed confirmed ORR was 24% (95% CI, 13−37). Median DOR was 4.2 months (range, 1.0^{+}−9.7); 4 patients responded for >8 months. The 6-month PFS rate was 29% (95% CI, 17−43). Independent review outcomes were comparable, with confirmed ORR of 22% (95% CI, 12−35), median DOR of 6.0 months (range, 1.0^{+}−9.7), and 6-month PFS rate of 40% (95% CI, 24−55). TF expression was confirmed in most patients; no significant association with response was observed.

Conclusions: Tisotumab vedotin demonstrated a manageable safety profile and encouraging antitumor activity in patients with previously treated recurrent/metastatic cervical cancer.

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Introduction

Cervical cancer is a common cancer in women, with an estimated 570,000 new cases globally in 2018, and represents the third-leading cause of cancer-related death in women worldwide.[1] Recurrent/metastatic cervical cancer (r/mCC) has a poor prognosis, with a 5-year survival rate of 17%.[2] Bevacizumab and doublet chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) was adopted as first-line (1L) standard-of-care therapy for r/mCC in the past 5 years.[3-5] However, nearly all patients relapse after 1L, and single institution experiences indicate that the percentage of patients who receive a second-line (2L) therapy varies (30-70%) as many patients die before receiving treatment.[6,7]

Available 2L+ therapies for r/mCC are characterized by low response rates.[4,5] Before adoption of bevacizumab+doublet chemotherapy in 1L, therapies administered in the 2L+ setting reported response rates in the range of 4.5-15%, with median survival <8 months.[8-14] Data in the post-bevacizumab+chemotherapy setting are limited, with a single-institution study showing single-digit response rates (0-6%) for 2L treatment,[6] suggesting prior vascular endothelial growth factor inhibition may negatively impact subsequent treatment response. Data in the third-line setting are further limited, with ≈60% of patients not receiving third-line treatment and, when treated, response rates of 3%.[7] Recently, pembrolizumab (anti–programmed death 1) was granted accelerated approval in the United States for the 2L+ treatment of patients with programmed death-ligand 1 (PD-L1)-positive (combined positive score ≥1%) r/mCC.[15] However, only patients with PD-L1–positive tumors are eligible and only a fraction of these patients respond (objective response rate [ORR], 14%).[15] In addition, efficacy in nonsquamous r/mCC is not yet known as 92% of the patients studied had squamous histology.[15] These data underscore the high

and immediate need for effective therapies that provide clinical benefit in a broader patient population.

Tisotumab vedotin (TV) is a first-in-class antibody-drug conjugate (ADC) composed of a tissue factor (TF)-specific, fully human monoclonal antibody conjugated to the clinically validated microtubule-disrupting agent monomethyl auristatin E (MMAE).[16,17] Under normal physiological conditions, TF is central to the coagulation pathway.[18] In oncogenesis, TF plays a role in tumor-associated angiogenesis, progression, and metastasis.[19-22] TF is aberrantly expressed across many solid tumors, including cervical cancer,[21,23-25] and has been associated with poor clinical outcomes.[21] The expression of TF across tumor types and its role in oncogenesis makes it an appealing therapeutic target.

TV delivers MMAE to TF-expressing cells to induce direct cytotoxicity and bystander killing of neighboring cells.[16,17] *In vitro* studies demonstrated that TV induces immunogenic cell death (ICD) and efficiently engages with immune cells to promote tumor cell death through Fcγ receptor-mediated effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).[17,26] Moreover, TV was found to inhibit TF-activated factor VII (FVIIa)-dependent intracellular signaling, while minimally impacting procoagulant activity.[17] To our knowledge, TV is the first and only drug to successfully target TF.

innovaTV 201 (NCT02001623) is a phase 1/2 dose-escalation and expansion trial evaluating TV in patients with previously treated locally advanced or metastatic solid tumors. In the dose-

escalation phase, TV showed a manageable safety profile, and 2.0 mg/kg every 3 weeks was established as the recommended phase 2 dose.[27] Here, we report the safety and antitumor activity of TV in the cervical cancer expansion cohort.

Methods

Study Oversight

Genmab A/S sponsored the study, provided study drug, and collaborated with academic investigators on study design, data analysis/interpretation, and manuscript writing. The trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, Declaration of Helsinki, and all applicable regulatory requirements. The trial protocol was approved by an independent ethics committee or institutional review board prior to initiation. All patients gave written informed consent. All authors confirm the accuracy of the data and adherence of the trial to the protocol.

Study Design and Patients

innovaTV 201 is an open-label, multi-cohort, phase 1/2 dose escalation and expansion study of TV in locally advanced and/or metastatic solid tumors known to express TF. The design of the innovaTV 201 study has been previously described (additional details in the Supplementary Appendix).[27]

A protocol amendment expanded the cervical cancer cohort to enroll a maximum of 55 patients in order to better characterize the activity and tolerability of TV in this population. Eligible patients had measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with known coagulation defects, ongoing major bleeding, or Common Toxicity Criteria for Adverse Events (CTCAE) grade ≥2 neuropathy were excluded. A protocol amendment allowed for enrollment of patients on anticoagulants. Patients in the cervical cancer cohort had

recurrent/metastatic disease, progressed on a platinum-based regimen, and received ≤4 prior treatments for advanced disease.

Treatment and Assessments

Patients in the cervical cancer cohort received TV 2.0 mg/kg intravenous infusion every 3 weeks for four cycles. Patients with clinical benefit (stable disease [SD] or better) at the end of four cycles had the option to continue treatment for an additional eight cycles (up to 12 cycles total), or until disease progression or unacceptable toxicity. After 12 cycles, patients with clinical benefit could continue in an extension study (NCT03245736).

Safety was monitored throughout the study and for up to 30 days after last dose. Adverse events (AEs) were graded according to the National Cancer Institute CTCAE v4.03 and coded according to Medical Dictionary for Regulatory Activities (MedDRA) v17.0. AEs of special interest (AESIs) for which pooled standardized MedDRA queries (SMQs) were applied included neuropathies (known MMAE-related AEs), bleeding-related events (because of TF's role in coagulation), and ocular events (conjunctivitis, conjunctival ulceration, keratitis, symblepharon) that were on-treatment AEs identified during dose escalation. Protocol amendments implementing mitigation measures to reduce the risk for ocular events were introduced throughout the study. These included application of lubricating, steroid, and vasoconstrictor eye drops, and cooling eye pads worn during infusion. Furthermore, the use of contact lenses was avoided, and stricter dose modification guidance for ocular events was provided.

Tumor responses were assessed by investigator and independent review committee (IRC) using magnetic resonance imaging or computed tomography scans at baseline and every 6 weeks during the study. Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response.

Fresh or archival tumor biopsies were requested upon enrollment from either primary or metastatic lesions in each patient and were retrospectively assessed for membrane and cytoplasmic TF tumor expression in a central laboratory using an analytically validated immunohistochemistry assay. TF histology-score (H-score) was calculated based on the percentage of tumor tissue that had membrane or cytoplasmic TF expression intensity of low (1+), intermediate (2+), and high (3+) on evaluable samples using the following equation: H-score = (1×[% cells 1+])+(2×[% cells 2+])+(3×[% cells 3+]).

Study Outcomes

The primary objective of this study was to evaluate the safety and tolerability of TV. Key secondary endpoints included ORR (defined as complete response [CR] or partial response [PR] as assessed by the investigator or IRC), duration of response (DOR), and progression-free survival (PFS) per RECIST v1.1.

Statistical Analyses

All patients who received at least one dose of TV were included in the safety and antitumor activity analyses. ORR was determined with a corresponding two-sided 95% exact binomial confidence interval (CI). IRC-assessment utilized a 2+1 adjudication method. Agreement

between investigator- and IRC-assessment with respect to confirmed objective response was determined using Cohen's kappa. Median PFS and DOR were determined using the Kaplan–Meier method and presented with a two-sided 95% CI. Prespecified subgroup factors included TF expression. Association between TF expression and response was analyzed using analysis of variance with Tukey's multi-comparison post hoc test.

Results

Patients

Between November 2015, and April 2018, a total of 55 patients were enrolled into the cervical cancer expansion cohort of the innovaTV 201 study (**Figure S1**). The demographics and baseline disease characteristics are presented in **Table 1**. Most patients had ECOG performance status of 1 (73%). 51% of the patients had squamous cell carcinoma and 35% had adenocarcinoma. 51% received ≥2 prior lines of treatment. Four patients did not receive 1L standard-of-care therapy because they were refractory to treatment for early stage disease (concurrent chemoradiation or neoadjuvant therapy) and were considered as having zero prior lines of treatment in the recurrent setting. Prior systemic therapies received included taxanes (91%) and bevacizumab+doublet chemotherapy (67%). TF expression (≥1%) was confirmed in the majority of evaluable patients (membrane expression, 100%; cytoplasmic expression, 96%).

Safety

At data cutoff (September 30, 2018), the median follow-up was 3.5 months (range, 0.6–11.8). The median number of doses of TV received was 4.0 (range, 1.0–14.0). Ten patients (18%) discontinued treatment due to an AE, the most common of which was peripheral neuropathy (9%). Seven patients (13%) had an AE leading to dose reduction (**Table S1**).

Treatment-emergent AEs regardless of causality and of any grade were reported in all patients, and AEs of grade ≥3 were reported in 31 patients (56%) (**Table 2**). The most common AEs were epistaxis (51%), fatigue (51%), nausea (49%), conjunctivitis (42%), and alopecia (40%) (**Table 2**). Of these, most were grade 1/2. The most common grade ≥3 AEs were anemia (11%), fatigue

(9%), and vomiting (7%). Twenty-nine patients (53%) had serious AEs (**Table S2**), the most common of which were vomiting (7%) and constipation (5%). Two fatal events occurred while on treatment, both due to disease progression, and were assessed as unrelated to treatment by investigator and study sponsor. No treatment-related deaths were observed.

No grade ≥4 AESIs were observed. Neuropathy AESIs occurred in 30 patients (55%), 6 of which (11%) were grade 3, and the most common was peripheral neuropathy (36%; grade 3, 4%) (**Table 2, Table S3**). Seventeen patients (31%) had neuropathy at baseline. Bleeding-related AESIs occurred in 40 patients (73%) and most were grade 1/2, with three patients (5%) experiencing a grade 3 bleeding-related event (two with vaginal hemorrhage and one with hematuria) (**Table 2, Table S4**). The most common bleeding-related event was epistaxis (51%); all were grade 1 except for one grade 2. Ocular AESIs of any type occurred in 36 patients (65%), and the most common were conjunctivitis (42%) and dry eye (24%) (**Table 2, Table S5**). The incidence of ocular events was reduced from 80% in patients enrolled prior to the implementation of mitigation measures (n=15) to 60% in patients enrolled after implementation (n=40). The rates of conjunctivitis were reduced from 80% to 28% (**Figure S2**).

Antitumor Activity

The investigator-assessed confirmed ORR was 24% (95% CI, 13−37) (**Table 3**). Maximum changes in target lesion size from baseline are shown in **Figure 1A**. The median time to response (TTR) was 2.6 months (range, 1.1−3.9) and the median DOR was 4.2 months (range, 1.0^{+}−9.7) (**Table 3**). Four patients experienced a confirmed PR for >8 months (**Figure 1B**). The median

PFS was 4.2 months (95% CI, 2.1−5.3), and the 6-month PFS rate was 29% (95% CI, 17−43) (**Table 3, Figure S3**).

The IRC-assessed confirmed ORR was 22% (95% CI, 12−35) (**Table 3**). One patient had CR by IRC-assessment. The overall agreement between investigator- and IRC-assessment with respect to ORR was 95% (Cohen's kappa 0.84). The median IRC-assessed DOR was 6.0 months (range, 1.0^{+}−9.7), and the 6-month PFS rate was 40% (95% CI, 24−55) (**Table 3, Figure S4**).

Figure 1C shows the target and non-target lesion baseline and follow-up scans of a 43-year-old female patient with squamous cell carcinoma previously treated with paclitaxel+carboplatin. This patient achieved PR after 16 weeks of treatment and discontinued TV due to an AE at that time. The decreased target lesion size persisted after treatment discontinuation up to week 47.

Subgroup and Biomarker Analysis

Investigator-assessed responses with TV were observed across histologic types (squamous cell carcinoma ORR, 29% [8/28 patients]; adenocarcinoma ORR, 16% [3/19]) and for patients who received zero (25% [1/4]), one (22% [5/23]), two (35% [6/17]), or 3-4 (9% [1/11]) prior lines of therapy (**Figure 2A**). Patients who previously received bevacizumab+doublet chemotherapy demonstrated a similar ORR to the overall population (22% [8/37]).

TF expression was evaluable in 46 of the 55 patients (84%), as three patients had no biopsy and six had insufficient tumor material. Of the evaluable cases, 39 patients (85%) had archival biopsies and seven (15%) had fresh biopsies. Twenty-nine biopsies (63%) were from primary

tumors and 17 (37%) were from metastatic lesions. Investigation of membrane or cytoplasmic TF expression (H-score) did not show a statistically significant association with investigator-assessed best overall confirmed response (**Figure 2B-C**).

Discussion

In patients with advanced r/mCC, TV, a first-in-class ADC designed to target TF, demonstrated a manageable safety profile and encouraging antitumor activity in a patient population for which no standard-of-care therapy exists. To our knowledge, TV is the first and only ADC to successfully demonstrate meaningful clinical activity specifically targeting TF, a novel therapeutic target overexpressed in many solid tumors associated with poor outcomes.

The safety profile of TV was generally consistent with other MMAE-based ADCs, except for epistaxis and conjunctivitis.[28,29] Almost all epistaxis events were grade 1, and none required clinical intervention. Moreover, as TF is highly expressed in the nasal epithelium,[30] this observation may reflect a local disruption of the nasal mucosa rather than an underlying treatment-induced coagulopathy. The incidence of other bleeding-related events was consistent with the expected incidence observed in patients with advanced cervical cancer. Most ocular events were grade 1/2, except for one patient with grade 3 conjunctivitis. The incidence of ocular events, including conjunctivitis, was reduced in the patients enrolled after implementation of mitigation measures. Although the mechanism of the ocular events is not known, TF expression has been demonstrated in the ocular epithelium,[31,32] which may result in treatment-emergent toxicity in these cells. The understanding of TF-related epistaxis and ocular events is continuing to evolve, and further studies are needed to optimize mitigation strategies, as well as to assess the long-term effects of TV, the duration of these AESIs, and the mechanisms by which they occur.

The ORR observed with TV across histological types, line of therapy, and prior treatments, including bevacizumab+doublet chemotherapy, is clinically important in a patient population

that lacks meaningful therapies for the treatment of their disease. TV demonstrated a high response rate and substantial 6-month PFS in 2L+ patients, including those with adenocarcinoma r/mCC. This is notable in comparison to efficacy of pembrolizumab in patients with PD-L1−positive tumors (ORR, 14%).[15] Furthermore, pembrolizumab efficacy in patients with nonsquamous histology has not been well established, and, while the median DOR was not reached, meaningful PFS benefit was not observed.[33]

The antitumor activity of TV is further supported by the concordance between the investigator- and IRC-assessed ORR and prolonged responses. The durability of response with TV is highlighted by the four patients with response >8 months and the patient case demonstrating persistent PR despite TV discontinuation. The durable responses observed may be indicative of the multiple mechanisms of action of TV, including direct cytotoxicity, bystander killing, and ICD induced by MMAE, as well as Fcγ receptor-mediated effector functions and inhibition of TF/FVIIa signaling.[16,17,26]

The majority of cervical cancer patient biopsies had detectable TF expression. Although median membrane and cytoplasmic TF H-score was higher in patients who achieved PR and SD compared to those with progressive disease, there was no statistically significant association with best confirmed response. That said, the majority of samples were from archival tissue, and the effect of previous lines of therapy on TF expression has yet to be explored.

This study demonstrated the antitumor activity of TV in patients with advanced, previously treated r/mCC. However, overall survival was not a specified endpoint, and thus further studies

are needed to establish the impact of TV on survival in these patients. The ongoing phase 2 innovaTV 204 study (NCT03438396; ENGOT-cx6; GOG-3032) is investigating the antitumor activity and safety of TV in ≈100 patients with previously treated r/mCC. Additionally, the phase 1/2 innovaTV 205 study (NCT03786081; ENGOT-cx8; GOG-3024) is investigating the combination of TV with pembrolizumab, bevacizumab, or carboplatin in the 1L and 2L+ settings in patients with r/mCC.

R/mCC is a serious, life-threatening disease. The lack of effective treatments, high relapse risk, and low survival after 1L treatment demonstrate the need for novel, safe, and effective therapies that improve clinical benefit. The results of this study cohort have demonstrated the manageable safety profile and encouraging antitumor activity of TV, supporting the further clinical development of this first-in-class ADC targeting the novel therapeutic target, TF, in patients with previously treated r/mCC.

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Data Sharing Statement

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 following 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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Figure Legends

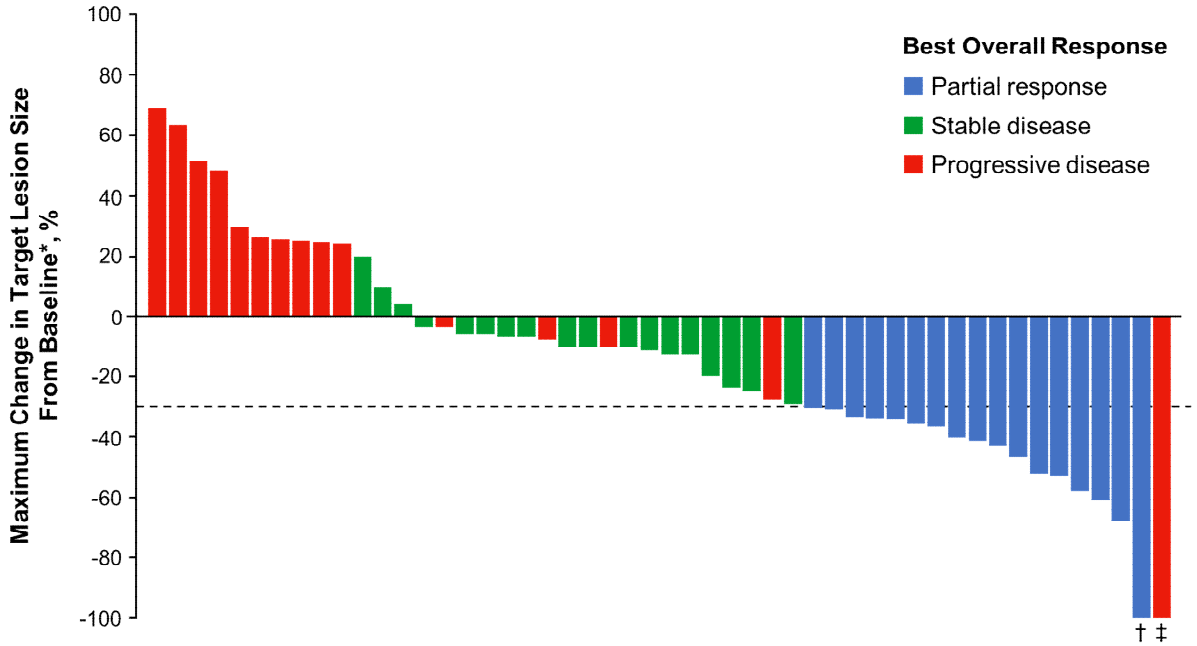
Figure 1. Investigator-Assessed Antitumor Activity of Tisotumab Vedotin in Patients With Cervical Cancer. Panel A shows the maximum percentage change from baseline in target lesion size as assessed by the investigator colored by best overall response. *Four patients did not have post-baseline scans and one patient did not have post-baseline assessments of sum of target lesions; these patients were excluded from this analysis. †Patient had lymph node disease and persistent non-target lesions; overall assessment was PR. ‡Patient had lymph node disease, persistent non-target lesions, and a new lesion; overall assessment was PD. Panel B depicts investigator-assessed time to response and duration of response for patients with confirmed PR as measured by RECIST v1.1 (n=13). Panel C shows target and non-target lesion scans at baseline and follow-up visits for a 43-year-old female patient with squamous cell carcinoma previously treated with paclitaxel and carboplatin. Weeks are measured from cycle 1 day 1 of tisotumab vedotin. The patient achieved a PR and discontinued tisotumab vedotin due to an adverse event at week 16 (black arrow). PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors v1.1.

Figure 2. Response Across Baseline Disease Characteristic Subgroups and by Tissue Factor Expression. Panel A shows the investigator-assessed confirmed ORR (95% CI) in patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; in patients who received 1, 2, or 3-4 prior lines of systemic treatment; and in patients who received prior taxanes, bevacizumab, or bevacizumab+doublet chemotherapy. *Investigator-assessed confirmed response by RECIST v1.1. †Patients with other histology (n=2) did not have confirmed response.

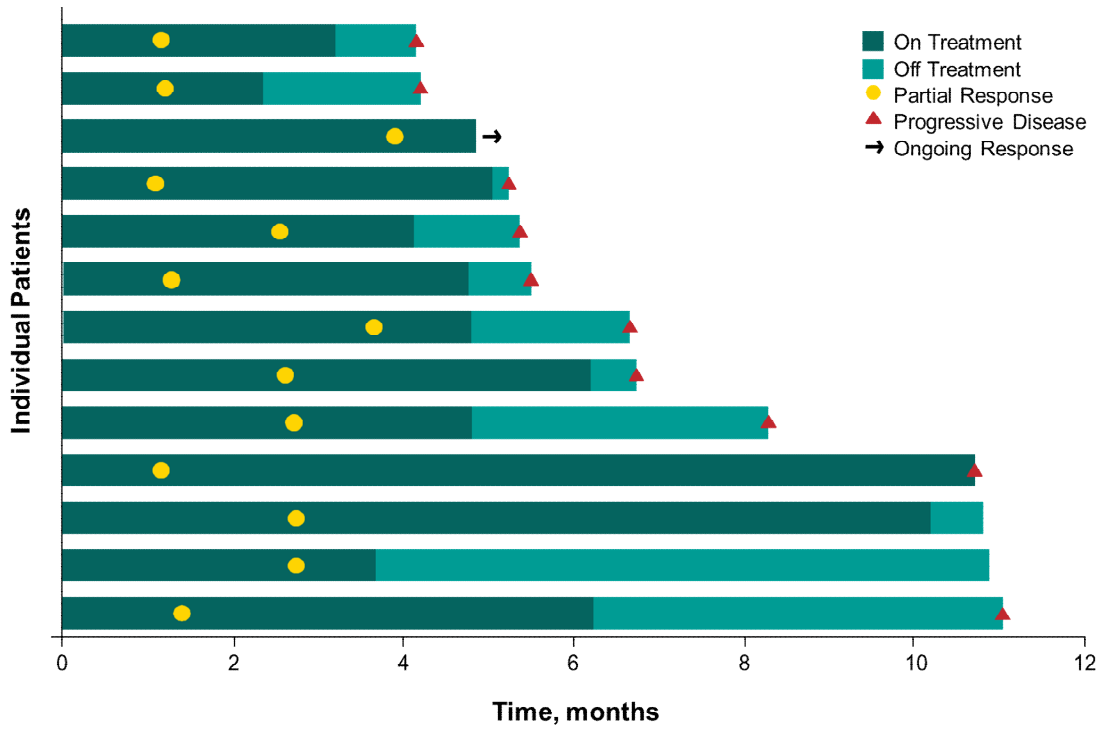
Panels B and C depict membrane (B) and cytoplasmic (C) TF expression intensity as measured by H-score, in patients who had investigator-assessed best confirmed PR, SD, or PD. *P* values are for descriptive purposes only. CI, confidence interval; H, histology; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors v1.1; SD, stable disease; TF, tissue factor.

Figure 1.

A


Maximum Change in Target Lesion Size From Baseline*, %
100
80
60
40
20
0
-20
-40
-60
-80
-100
Best Overall Response
Partial response
Stable disease
Progressive disease
† ‡

B


Individual Patients
On Treatment
Off Treatment
Partial Response
Progressive Disease
Ongoing Response
0
2
4
6
8
10
12
Time, months

C

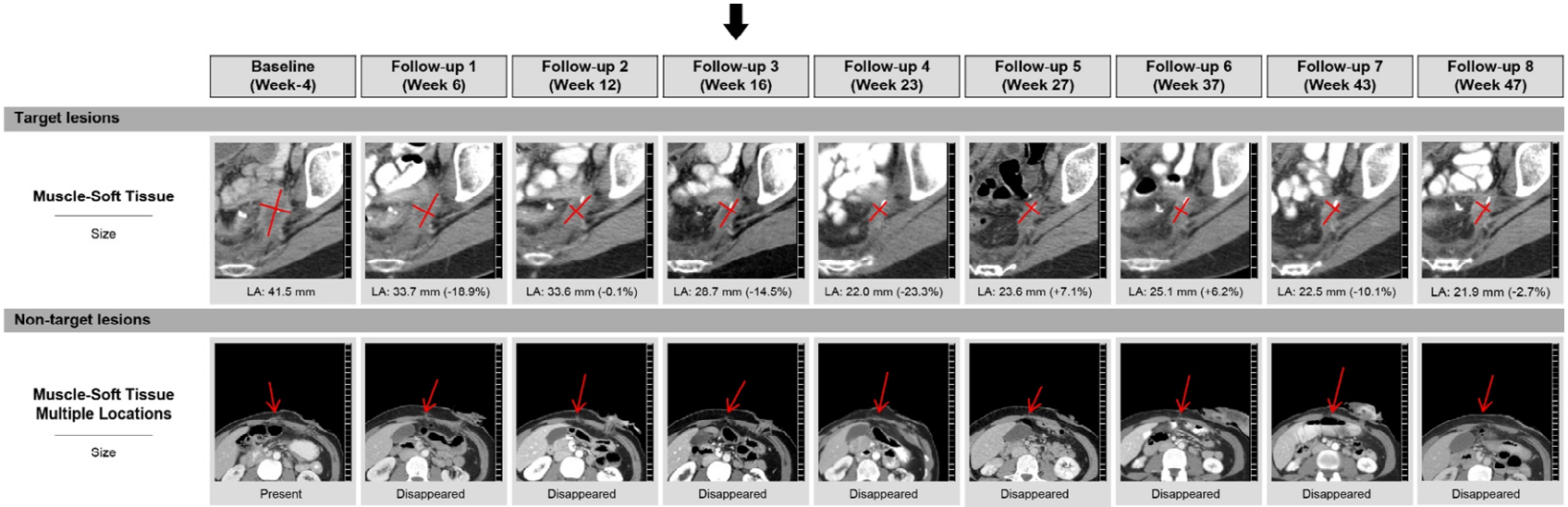
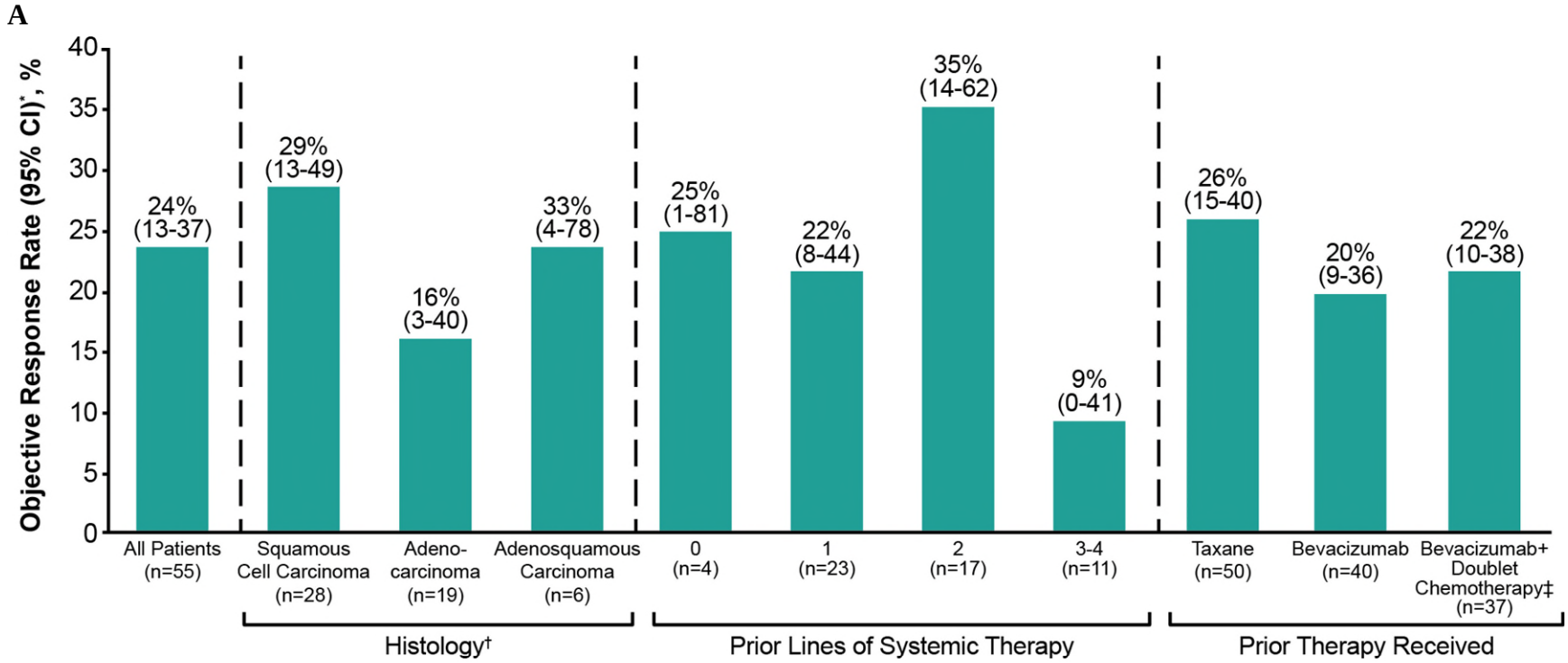
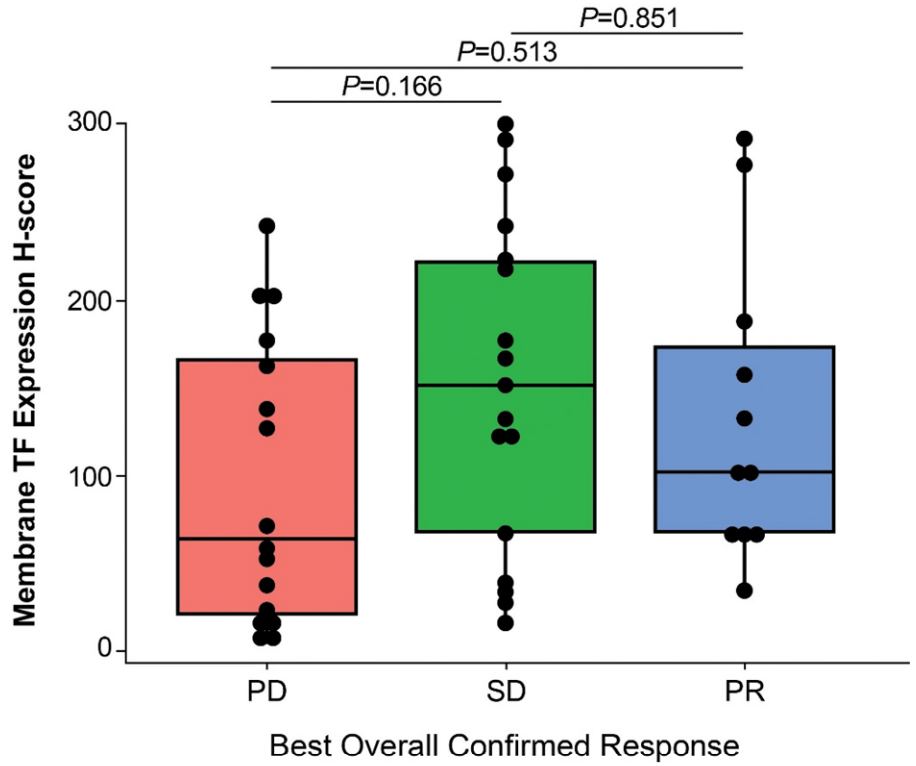

Baseline (Week-4)
Follow-up 1 (Week 6)
Follow-up 2 (Week 12)
Follow-up 3 (Week 16)
Follow-up 4 (Week 23)
Follow-up 5 (Week 27)
Follow-up 6 (Week 37)
Follow-up 7 (Week 43)
Follow-up 8 (Week 47)
Target lesions
Muscle-Soft Tissue
Size
LA: 41.5 mm
LA: 33.7 mm (-18.9%)
LA: 33.6 mm (-0.1%)
LA: 28.7 mm (-14.5%)
LA: 22.0 mm (-23.3%)
LA: 23.6 mm (+7.1%)
LA: 25.1 mm (+6.2%)
LA: 22.5 mm (-10.1%)
LA: 21.9 mm (-2.7%)
Non-target lesions
Muscle-Soft Tissue Multiple Locations
Size
Present
Disappeared
Disappeared
Disappeared
Disappeared
Disappeared
Disappeared
Disappeared
Disappeared

Figure 2.


A
Objective Response Rate (95% CI)*, %
40
35
30
25
20
15
10
5
0
24% (13-37)
29% (13-49)
16% (3-40)
33% (4-78)
25% (1-81)
22% (8-44)
35% (14-62)
9% (0-41)
26% (15-40)
20% (9-36)
22% (10-38)
All Patients (n=55)
Squamous Cell Carcinoma (n=28)
Adeno-carcinoma (n=19)
Adenosquamous Carcinoma (n=6)
0 (n=4)
1 (n=23)
2 (n=17)
3-4 (n=11)
Taxane (n=50)
Bevacizumab (n=40)
Bevacizumab+ Doublet Chemotherapy‡ (n=37)
Histology†
Prior Lines of Systemic Therapy
Prior Therapy Received

B


P=0.851
P=0.513
P=0.166
300
200
100
0
Membrane TF Expression H-score
PD
SD
PR
Best Overall Confirmed Response

C

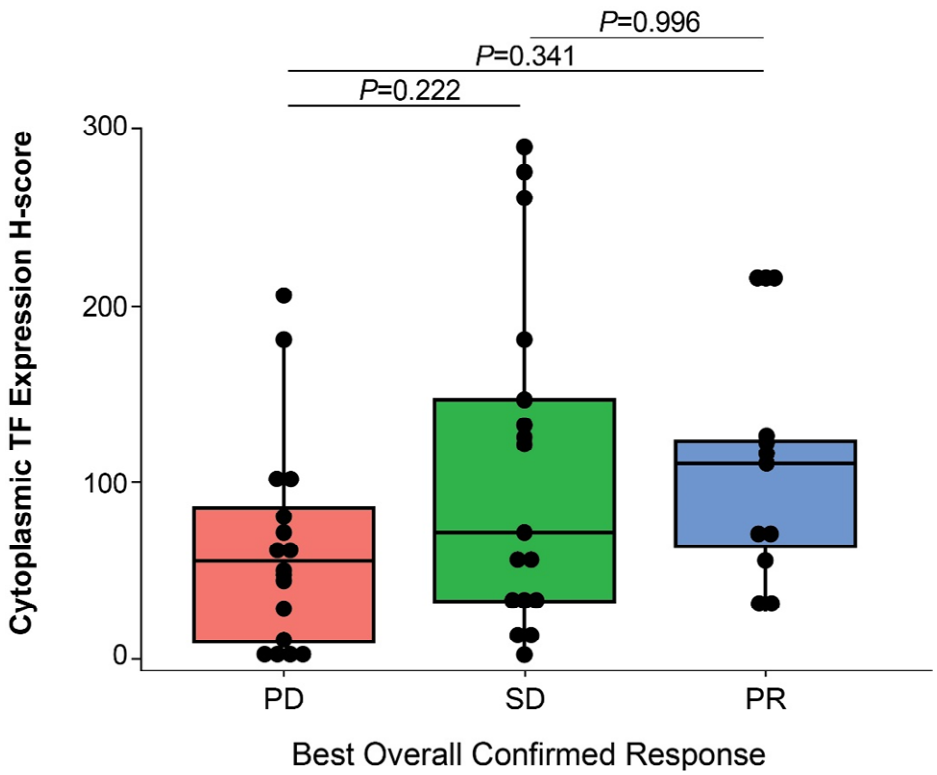

P=0.996
P=0.341
P=0.222
300
200
100
0
Cytoplasmic TF Expression H-score
PD
SD
PR
Best Overall Confirmed Response

Table 1. Baseline Demographics and Disease Characteristics.

	Cervical Cancer Cohort N=55
Age, median (range), years	46 (21–73)
Race, n (%)*	
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 cell carcinoma	28 (51)
Adenocarcinoma	19 (35)
Adenosquamous carcinoma	6 (11)
Other†	2 (4)
Prior lines of systemic therapies for recurrent/metastatic disease, n (%)	
0‡	4 (7)
1	23 (42)
2	17 (31)
3	6 (11)
4	5 (9)

Prior systemic therapies received, n (%)	
Taxane	50 (91)
Bevacizumab	40 (73)
Bevacizumab+doublet chemotherapy§	37 (67)
TF expression positive, n (%)‖	
Membrane	46 (100%)
Cytoplasm	44 (96%)

ECOG, Eastern Cooperative Oncology Group; TF, tissue factor.

* Two patients were missing race information; percentage prevalence was calculated out of n=53 for race.

† Following the data cutoff date, patients with other histology were resolved as having adenosquamous (n=1) and neuroendocrine (n=1) histology.

‡ Patients did not receive standard-of-care therapy in the first-line recurrent setting because they were refractory to treatment administered for early-stage disease (concurrent chemoradiation therapy or neoadjuvant therapy).

§ Doublet chemotherapy defined as paclitaxel+cisplatin or paclitaxel+topotecan.

‖ Positive TF expression was defined as ≥1%; percentage prevalence was calculated out of TF expression evaluable population (n=46).

Table 2. Treatment-Emergent Adverse Events.

Incidence, n (%)	Cervical Cancer Cohort N=55	
	All-grade	**Grade ≥3**
Patients with ≥1 AE	55 (100)	31 (56)
AEs With ≥20% Incidence	**All-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	20 (36)	2 (4)
Vomiting	19 (35)	4 (7)
Diarrhea	16 (29)	1 (2)
Abdominal pain	15 (27)	3 (5)
Anemia	13 (24)	6 (11)
Dry eye	13 (24)	0
Hypokalemia	11 (20)	3 (5)
Pruritus	11 (20)	0
Pyrexia	11 (20)	1 (2)
Urinary tract infection	11 (20)	1 (2)
AESIs with ≥5% Incidence	**All-grade**	**Grade 3**

Neuropathy AESIs*		
Peripheral neuropathy	20 (36)	2 (4)
Muscular weakness	4 (7)	0
Peripheral sensory neuropathy	4 (7)	0
Bleeding-related AESIs†		
Epistaxis	28 (51)	0
Vaginal hemorrhage	7 (13)	2 (4)
Hematuria	5 (9)	1 (2)
Contusion	3 (5)	0
Ocular AESIs‡		
Conjunctivitis	23 (42)	1 (2)
Dry eye	13 (24)	0
Ulcerative keratitis	4 (7)	0
Blepharitis	3 (5)	0
Keratitis	3 (5)	0

AE, adverse event; AESI, adverse event of special interest; SMQ, standardized Medical Dictionary for Regulator Activities queries.

* Defined as peripheral neuropathy SMQ.

† Defined as hemorrhage SMQ.

‡ Defined as conjunctival disorders SMQ, corneal disorders SMQ, scleral disorders SMQ, retinal disorders SMQ, periorbital disorders SMQ, ocular infections SMQ, and optic nerve disorders SMQ.

Table 3. Investigator- and Independent Review Committee–Assessed Antitumor Activity of Tisotumab Vedotin.

	Cervical Cancer Cohort N=55	
	Investigator-assessed	**IRC-assessed**
ORR (95% CI), %*	24 (13–37)	22 (12–35)
CR, n (%)	0	1 (2)
PR, n (%)	13 (24)	11 (20)
SD, n (%)	21 (38)	19 (35)
Non-CR/Non-PD, n (%)	0	2 (4)
PD, n (%)	17 (31)	17 (31)
Not evaluable, n (%)	4 (7)	5 (9)
Median TTR (range), months	2.6 (1.1–3.9)	2.1 (1.1–4.6)
Median DOR (range), months	4.2 (1.0^{+}–9.7)	6.0 (1.0^{+}–9.7)
Median PFS (95% CI), months	4.2 (2.1–5.3)	4.1 (1.7–6.7)
6-month PFS rate, % (95% CI)	29 (17–43)	40 (24–55)

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

+ Indicates censored value due to ongoing response.

*Confirmed ORR by Response Evaluation Criteria In Solid Tumors v1.1 criteria.

Supplementary Appendix for "Tisotumab Vedotin in Previously Treated Recurrent/Metastatic Cervical Cancer"

David S. Hong, Nicole Concin, Ignace Vergote, Johann S. de Bono, Brian M. Slomovitz, Yvette Drew, Hendrik-Tobias Arkenau, Jean-Pascal Machiels, James F. Spicer, Robert Jones, Martin David Forster, Nathalie Cornez, Christine Gennigens, Melissa L. Johnson, Fiona C. Thistlethwaite, Reshma A. Rangwala, Srinivas Ghatta, Kristian Windfeld, Jeffrey R. Harris, Ulrik Niels Lassen, Robert L. Coleman

Content:

Supplementary Methods

The dose escalation phase of the innovaTV 201 study followed a standard 3+3 design to evaluate tisotumab vedotin at doses of 0.3 mg/kg up to 2.2 mg/kg administered intravenously every 3 weeks. The dose of tisotumab vedotin used in the expansion cohort was based on the safety and efficacy data from the dose escalation phase.[27]

The expansion phase included patients with locally advanced and/or metastatic cervical, ovarian, prostate, bladder, esophageal, endometrial, and non–small cell lung cancer who have progressed on or are ineligible for standard treatments.[27] The cervical and ovarian cancer cohorts were expanded from the initial 14 patients to approximately 30 patients each based on preliminary clinical activity and safety observed. After an amendment to the protocol, up to an additional 25 patients could be enrolled in the cervical cancer cohort for a maximum of 55 patients in total.

Figure S1. Patient Disposition in the Cervical Cancer Cohort of the innovaTV 201 Trial.

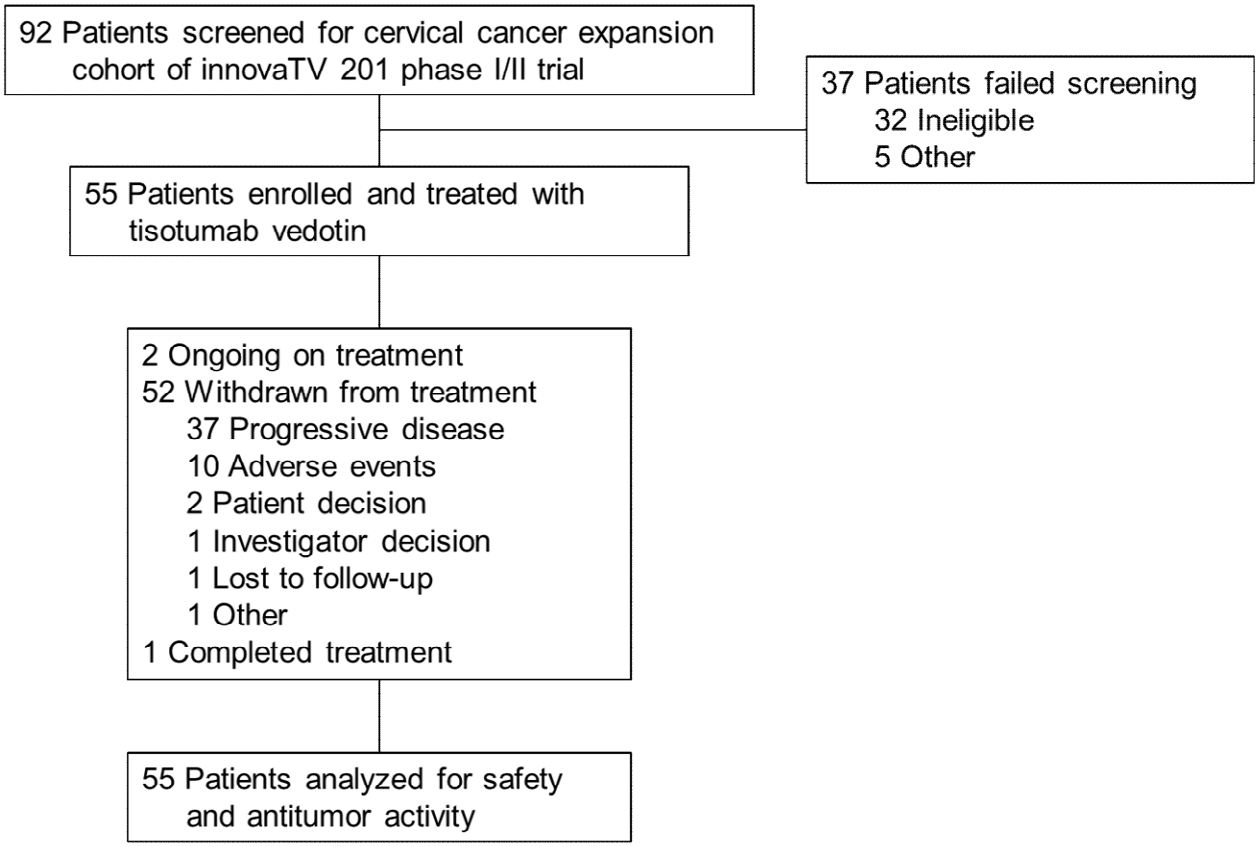


Figure S2. Conjunctivitis Before and After Mitigation Measures. The percentage incidence of conjunctivitis by grade occurring in patients enrolled before and after the implementation of mitigation measures are shown. *One patient with grade 3 conjunctivitis after mitigation measures were implemented. No grade 3 events were observed before mitigation measures were implemented.

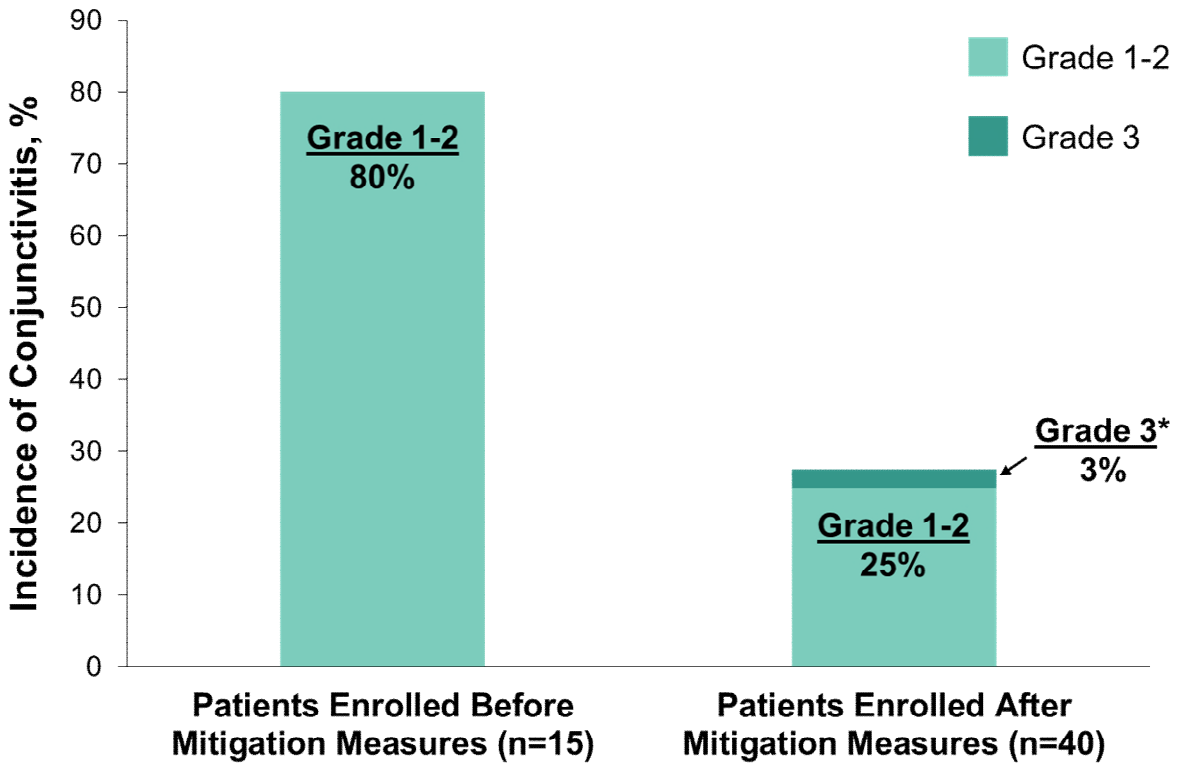


Figure S3. Investigator-Assessed Progression-Free Survival. The Kaplan–Meier curve for investigator-assessed progression-free survival for all patients in the cervical cancer cohort is shown.

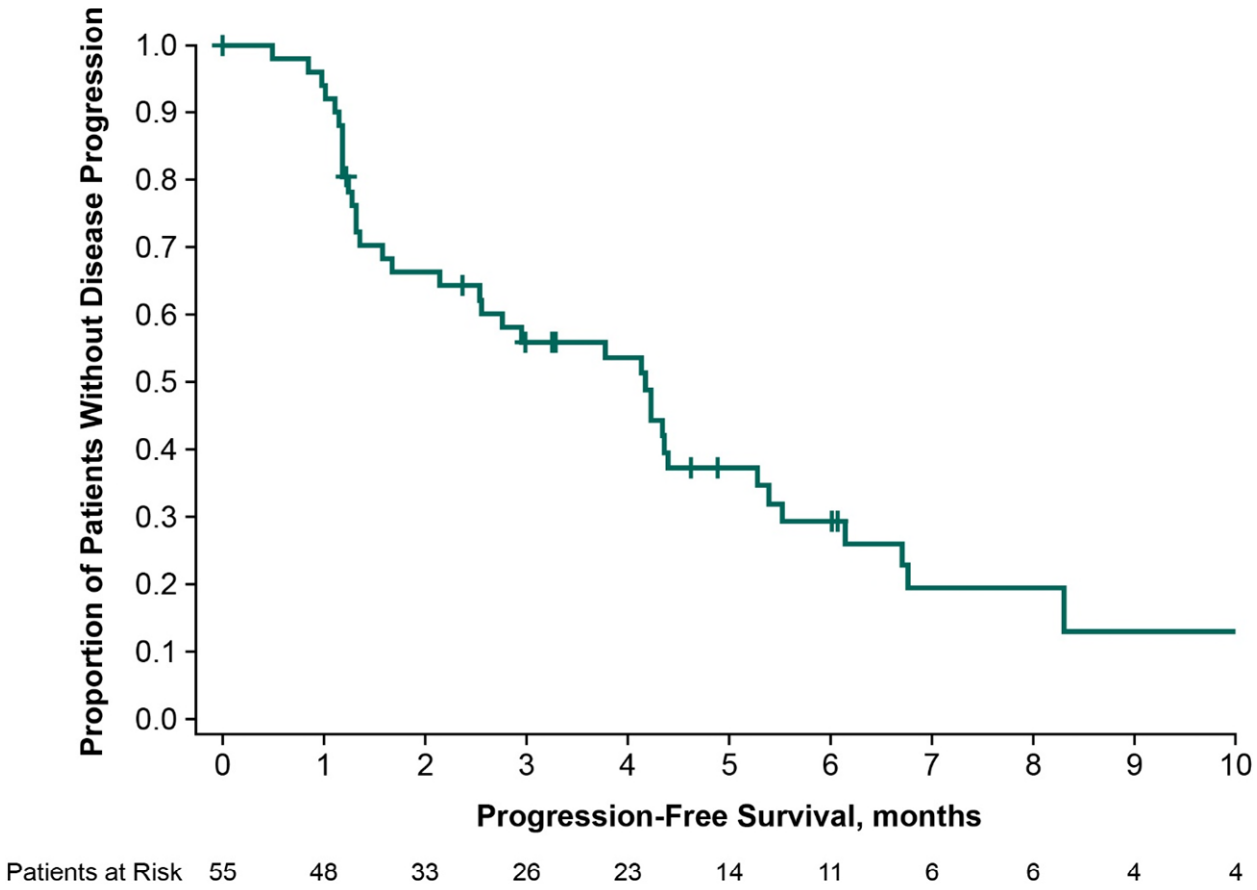
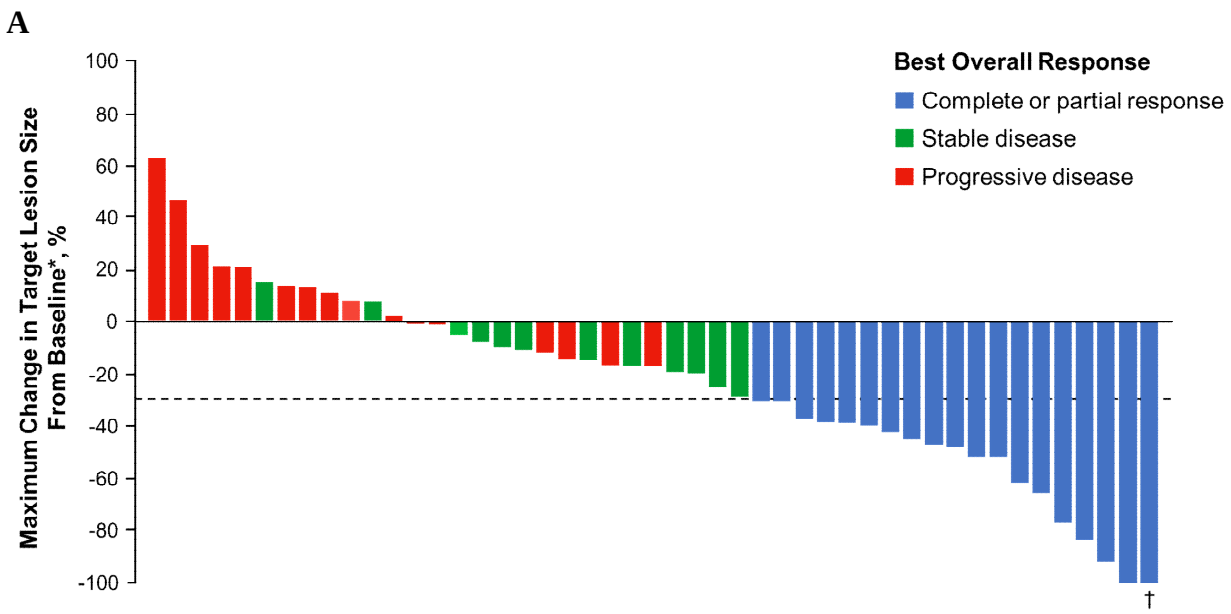
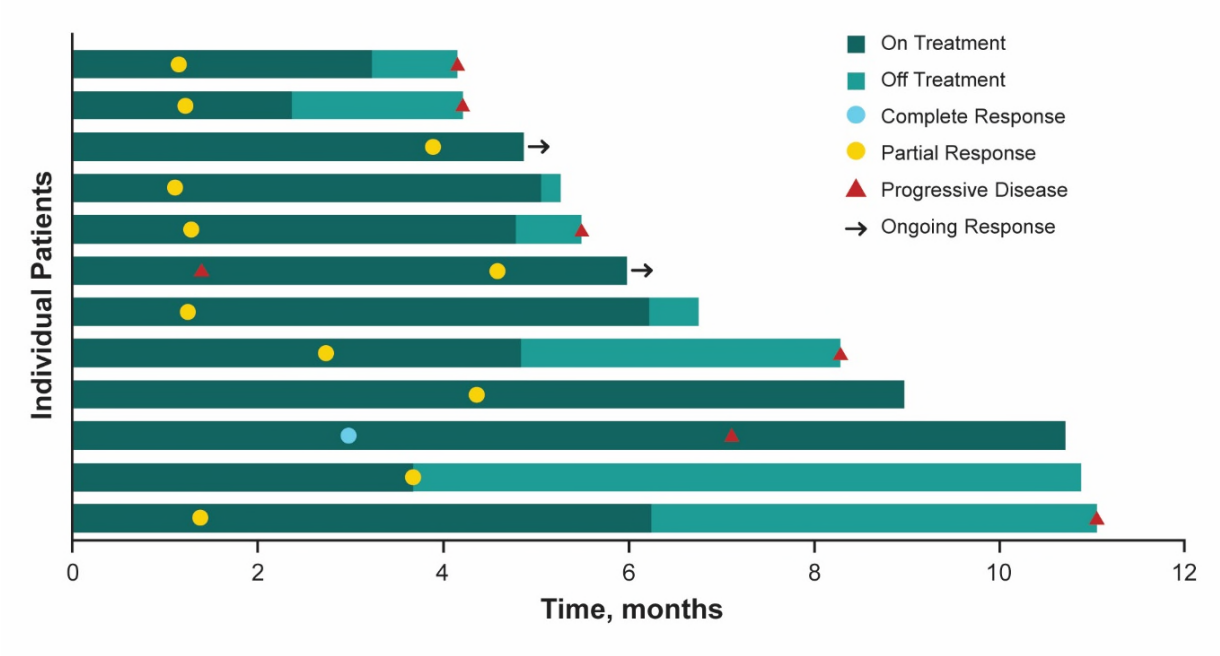


Figure S4. Independent Review Committee–Assessed Antitumor Activity of Tisotumab Vedotin in Patients With Cervical Cancer. Panel A shows the maximum percentage change from baseline in target lesion size as assessed by IRC colored by best overall response. *Eight patients did not have post-baseline scans and were excluded from this analysis. †Patient had overall assessment of CR. Panel B depicts IRC-assessed time to response and duration of response for patients with confirmed CR (n=1) and PR (n=11) as measured by RECIST v1.1. Panel C shows the Kaplan–Meier curve for investigator-assessed progression-free survival for all patients in the cervical cancer cohort is shown. CR, complete response; IRC, independent review committee; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors v1.1.



B


On Treatment
Off Treatment
Complete Response
Partial Response
Progressive Disease
Ongoing Response
Individual Patients
0
2
4
6
8
10
12
Time, months

C

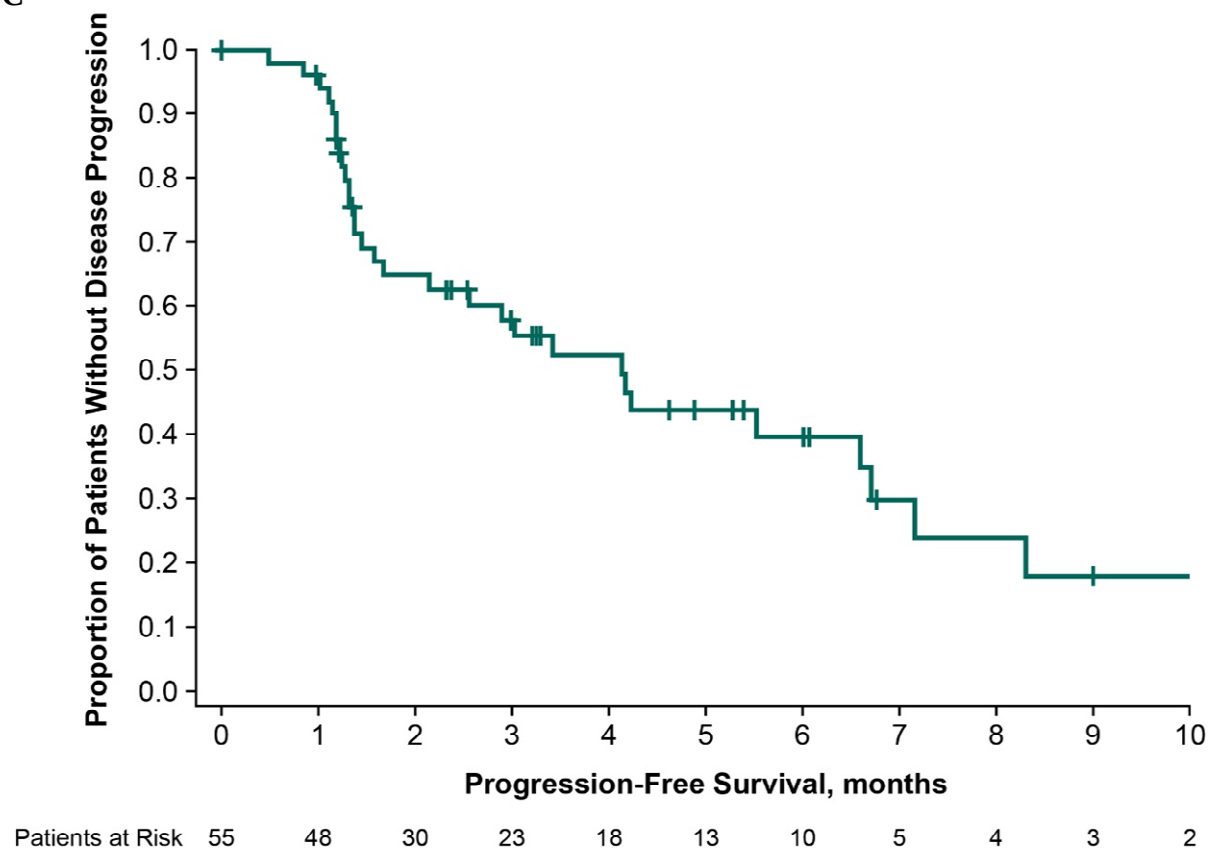

Proportion of Patients Without Disease Progression
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
8
9
10
Progression-Free Survival, months
Patients at Risk 55 48 30 23 18 13 10 5 4 3 2

Table S1. Adverse Events Leading to Treatment Discontinuation or Dose Reduction.

Incidence, n (%)	Cervical Cancer Cohort N=55
Patients with AEs leading to treatment discontinuation	**10 (18)**
Peripheral neuropathy	5 (9)
Conjunctivitis	2 (4)
Arthralgia	1 (2)
Corneal thinning	1 (2)
Peripheral motor neuropathy	1 (2)
Peripheral sensorimotor neuropathy	1 (2)
Ulcerative keratitis	1 (2)
Visual acuity reduced	1 (2)
Patients with AEs leading to dose reduction	**7 (13)**
Conjunctivitis	3 (5)
Conjunctival disorder	1 (2)
Deep vein thrombosis	1 (2)
Meibomianitis	1 (2)
Ulcerative keratitis	1 (2)

AE, adverse event.

Table S2. Serious Adverse Events.

Incidence, n (%)	Cervical Cancer Cohort N=55
Patients with ≥1 serious AE	**29 (53)**
Vomiting	4 (7)
Constipation	3 (5)
Abdominal pain	2 (4)
Anemia	2 (4)
Nausea	2 (4)
Peripheral sensorimotor neuropathy	2 (4)
Pyrexia	2 (4)
Urinary tract infection	2 (4)
Urinary tract obstruction	2 (4)
Vaginal hemorrhage	2 (4)
Acute kidney injury	1 (2)
Anxiety	1 (2)
Back pain	1 (2)
Bacterial sepsis	1 (2)
Catheter site pain	1 (2)
Device-related infection	1 (2)
Diarrhea	1 (2)
Disease progression	1 (2)
DISEASE PROGRESSION	1 (2)

Dysphagia	1 (2)
Dyspnea	1 (2)
Female genital tract fistula	1 (2)
Gastroenteritis	1 (2)
Hematuria	1 (2)
Headache	1 (2)
Hypokalemia	1 (2)
Hypoxia	1 (2)
Infection	1 (2)
Large intestinal obstruction	1 (2)
Lethargy	1 (2)
Malaise	1 (2)
Micrococcus infection	1 (2)
Pyelonephritis	1 (2)
Staphylococcal infection	1 (2)
Stent malfunction	1 (2)
Stress fracture	1 (2)
Supraventricular extrasystoles	1 (2)
Tumor pain	1 (2)
Urosepsis	1 (2)

AE, adverse event.

Table S3. Neuropathy Adverse Events of Special Interest.*

Incidence, n (%)	Cervical Cancer Cohort N=55	
	All-grade	Grade 3
Patients with ≥1 neuropathy AESI	**30 (55)**	**6 (11)**
Peripheral neuropathy	20 (36)	2 (4)
Muscular weakness	4 (7)	0
Peripheral sensory neuropathy	4 (7)	0
Hypoesthesia	2 (4)	0
Paresthesia	2 (4)	0
Peripheral sensorimotor neuropathy	2 (4)	2 (4)
Demyelinating polyneuropathy	1 (2)	1 (2)
Dysesthesia	1 (2)	0
Gait disturbance	1 (2)	0
Peripheral motor neuropathy	1 (2)	1 (2)

AESI, adverse event of special interest; SMQ, standardized Medical Dictionary for Regulatory Activities queries.

* Defined as peripheral neuropathy SMQ.

Table S4. Bleeding-Related Adverse Events of Special Interest.*

Incidence, n (%)	Cervical Cancer Cohort N=55	
	All-grade	Grade 3
Patients with ≥1 bleeding-related AESI	**40 (73)**	**3 (5)**
Epistaxis	28 (51)	0
Vaginal hemorrhage	7 (13)	2 (4)
Hematuria	5 (9)	1 (2)
Contusion	3 (5)	0
Rectal hemorrhage	2 (4)	0
Genital hemorrhage	1 (2)	0
Hematochezia	1 (2)	0
Hemorrhage	1 (2)	0
Menorrhagia	1 (2)	0
Pulmonary hemorrhage	1 (2)	0
Stroma site hemorrhage	1 (2)	0

AESI, adverse event of special interest; SMQ, standardized Medical Dictionary for Regulatory Activities queries.

* Defined as hemorrhage SMQ.

Table S5. Ocular Adverse Events of Special Interest.*

Incidence, n (%)	Cervical Cancer Cohort N=55	
	All-grade	Grade 3
Patients with ≥1 ocular AESI	**36 (65)**	**1 (2)**
Conjunctivitis	23 (42)	1 (2)
Dry eye	13 (24)	0
Ulcerative keratitis	4 (7)	0
Blepharitis	3 (5)	0
Keratitis	3 (5)	0
Conjunctival ulcer	2 (4)	0
Vision blurred	2 (4)	0
Vital dye staining cornea present	2 (4)	0
Conjunctival disorder	1 (2)	0
Conjunctival hyperemia	1 (2)	0
Conjunctival scar	1 (2)	0
Corneal irritation	1 (2)	0
Corneal thinning	1 (2)	0
Erythema of eyelid	1 (2)	0
Eye irritation	1 (2)	0
Eye nevus†	1 (2)	0
Meibomianitis	1 (2)	0
Ophthalmological examination abnormal	1 (2)	0
Punctate keratitis	1 (2)	0

Trichiasis	1 (2)	0
Visual acuity reduced	1 (2)	0

AESI, adverse event of special interest; SMQ, standardized Medical Dictionary for Regulatory Activities queries.

* Defined as conjunctival disorders SMQ, corneal disorders SMQ, scleral disorders SMQ, retinal disorders SMQ, periorbital disorders SMQ, ocular infections SMQ, and optic nerve disorders SMQ.

† One patient with occurrence of eye nevus was not graded.