Tisotumab vedotin-TFTV (TIVDAK) for Cervical Cancer
National Drug Monograph
November 2025
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Tisotumab vedotin-TFTV (TV) is a tissue factor-directed antibody drug conjugate (ADC) comprised of human anti-TF IgG1-kappa antibody conjugated to the microtubule disrupting agent monomethyl auristatin E (MMAE). The ADC binds to tissue-factor (TF) expressing cancer cells and is internalized where MMAE is cleaved and disrupts the microtubule network leading to apoptotic cell death
Indication Under Review[1]	Treatment of adults patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy
Dosage Regimen	Intravenous infusion of 2 mg/kg (max 200mg) every 3 weeks until disease progression or unacceptable toxicity. Requires premedication with corticosteroid eye drops TID x 72 hours after each infusion and topical vasoconstrictor drops immediately prior to each infusion.
Dosage Forms Under Review	Single-dose vial with 40mg lyophilized powder for reconstitution and dilution and intravenous infusion

EFFICACY CONSIDERATIONS

Trial	**innovaTV 204/GOG-3023/ENGOT-cx6 (NCT03438396) Phase 2**	**innovaTV 301 / ENGOT-cx12 / GOG-3057 (NCT04697628) Phase 3**
Design	Single-arm trial (n=101)	Randomized (1:1), open-label trial (n=502)
Population	Adults – recurrent or metastatic cervical cancer (squamous, adenosquamous or adenocarcinoma) with progression during/after doublet chemo plus bevacizumab if eligible, < 3 previous systemic regimens, ECOG PS 0 or 1	Adults with recurrent or metastatic squamous-cell, adenosquamous or adenocarcinoma with ECOG PS 0 or 1, measurable disease and life-expectancy ≥ 3 months. Required disease progression on previous standard of care chemotherapy doublet (paclitaxel + cisplatin, carboplatin or topotecan) along with bevacizumab and an anti-PD-1 or anti-PD-L1 (if both were available and patients were eligible for them).
Intervention	TV 2 mg/kg (maximum 200mg) TV q3 weeks until progressive disease or unacceptable toxicity	1:1 randomization TV 2 mg/kg (max 200mg) every 3 weeks until disease progression or unacceptable toxicity
Comparator	None	Investigators's choice of topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed
Demographic	• mAge 50 yrs (IQR 43-58); 95% white • Majority squamous cell (68%) or adenocarcinoma (27%) with 5% adenosquamous carcinoma • 60% had recurrent disease, 70% had 1 prior line of systemic therapy, 30% had 2. • Prior cisplatin + radiation: 54% • Prior bevacizumab + doublet chemo: 63% • Responsive to last systemic regimen: 38%	• mAge 51 (range 26-80) vs. 50 (range 27-78), • 48% and 49% white, 36% and 36% Asian, and 2% and 2% black • Histology: squamous cell carcinoma 63% vs. 63%, adenocarcinoma 34% vs. 30%, adenosquamous carcinoma 3% vs. 7% • Extrapelvic metastatic disease (90% and 90%) • ECOG PS 0 (54% vs. 55%), 1 (46% vs. 45%) • Prior lines of therapy: 1 (63% vs. 60%), 2 (37% vs. 40%) • Previous bevacizumab (65% vs. 63%) Previous anti-PD-1 or anti-PD-L1 (28% vs. 27%)
Results	**Outcomes** • Objective response rate (ORR), complete response (CR) partial response (PR), stable disease (SD), progressive disease or not evaluable (PD/NE). • Disease control rate (DCR) • Progression free and overall survival (PFS, OS) • 6 and 12 month PFS and OS	**Outcomes:** OS, investigator assessed progression-free survival (PFS), ORR (CR, PR, SD, PD) in ITT population, DOR

Outcome	TV (n=101)
ORR (95% CI)	24%, (95%CI 16, 33)

Outcome	TV (n=253)	Chemo (n=249)	HR (95% CI) / P value
mOS, mos. (95% CI)	11.5 (9.8, 14.9)	9.5 (7.9, 10.7)	0.7 (0.54, 0.89) P= 0.004
mPFS, mos. (95% CI)	4.2 (4, 4.4)	2.9 (2.6, 3.1)	0.67 (0.54, 0.82) P<0.001
ORR	18% (36, 49)	5% (12, 22)	OR 4.0 (2.1, 7.6)

CR PR SD PD/NE	7% 17% 49% 28%
DCR	72% (95% CI 63, 81)
DOR	8.3 (4.2 – NR)
PFS	4.2 mo (95% CI 3, 4.4)
OS	12 mo (95% CO 10, 14)
6, 12 mo OS	79% and 51%

(95% CI)			P<0.001
mDOR, mos.	5.3 (4.2, 8.3)	5.7 (2.8, not reached)	0.62 (0.4, 0.97)

SAFETY CONSIDERATIONS

Boxed Warnings	Ocular toxicity – conduct ophthalmologic exam prior to initiation, prior to every cycle for 9 cycles and as clinically indicated (visual acuity, slit lamp anterior eye and eye movement). Patients should use ophthalmic corticosteroids prior to each infusion and for 72 hours after each dose, and ophthalmic vasoconstrictor drops immediately prior to each infusion. Other care includes cold packs during infusion and frequent use of lubricating eye drops. Patients should avoid contact lenses entire duration therapy. Ocular toxicity may require dose modification **Ocular AEs**: 55% of patients across clinical trials, including conjunctivitis (32%), dry eye (24%), keratopathy (17%) and blepharitis (5%). Grade 3 in 3.3%, including ulcerative keratitis, corneal erosion, conjunctival ulcer and erosion and symblepheron (<2% for each). Median onset 1.2 mos. Complete resolution 59%, partial 31%. Ocular AEs led to permanent discontinuation in 6% of patients. In the phase 3 trial, AEs included conjunctivitis (31%), keratitis (16%) and dry eye (13%), grade 3 in 0.8%, including some delayed > 30 days after discontinuation. New or worsening symptoms should be referred to an eye care provider. See prescribing information for recommended preventative care and dose adjustments for toxicity.
Contraindications	None
Other Warnings	**Pneumonitis:** symptoms hypoxia, cough, dyspnea, infiltrates. Across clinical trials, 1% of patients, with one fatal case. TV dose should be withheld for persistent or recurrent Grade 2 and discontinued permanently in those with Grade 3 or 4. **Peripheral neuropathy**: 39% (6% Grade 3) across trials. Median onset 2.4 months (range 0-11). Complete resolution 18%, partial 21%. Led to drug discontinuation in 7%. Depending on severity withhold or reduce doses or and permanently discontinue for Grade 3 or 4. **Hemorrhage**: 51% of patients, epistaxis most common (33%). Grade 3 in 4%. Median onset 0.3 months. Complete resolution 71% and partial 12%. Permanently discontinue for pulmonary or central nervous system hemorrhage. For other types of bleeding, see prescribing information for recommendations on dose adjustments or discontinuation. **Severe cutaneous adverse reactions (SCAR)**: SCAR (including fatal or life-threatening Steven's Johnson Syndrome) can occur. SCAR in 1.6% of patients across clinical trials (0.5% ≥ grade 3, 1 case fatal). Patients should be monitored for skin lesions or blistering, sores in the mucous membranes or flu-like symptoms and swollen lymph nodes and permanently discontinued for confirmed Grade 3 or 4. **Embryo-fetal toxicity**: embryo-fetal harm possible when administered to pregnant woman. Patients should be advised of risks to a fetus and persons of reproductive potential advised to use effective contraception during treatment and for 2 months after the last dose.
Top 5 AEs	Occurring ≥ 25% of patients in pooled safety data at FDA approved dose: decreased hemoglobin (45%), peripheral neuropathy (39%), conjunctival AE (38%), nausea (37%), fatigue (36%), increased AST / ALT (33% and 30%), alopecia (31%), epistaxis (33%) and hemorrhage (28%). In innovaTV 301 (Phase 3), SAEs 33% of patients (most common UTI, small intestinal obstruction, sepsis, abdominal pain, hemorrhage). AEs led to dose interruption (39%), dose reduction (30%) and

	discontinuation (15%). Fatal AEs in 1.6% (1 case each of acute kidney injury, pneumonia, sepsis and Stevens-Johnson syndrome). Lower rates of decreased hemoglobin / neutrophils than chemotherapy. Similar results innovaTV 204 (Phase 2). SAEs 43%. Led to discontinuation (13%), dose interruption (47%), dose reduction (23%). Fatal AEs 4% (1 case each septic shock, pneumonitis, sudden death, multisystem organ failure). In both trials, peripheral neuropathy and ocular AEs were common causes of dose interruption, reduction and discontinuation. Infection, hemorrhage and ileus/intestinal obstruction less commonly.
Drug Interactions	MMAE is a CYP3A4 substrate. Monitor TV closely with strong CYP3A4 inhibitors for increased AEs.

VHA PLACE IN THERAPY

Cervical cancer has a poor prognosis, with 5-year overall survival less than 19% with distant metastases. Newer immunotherapies (anti-PD-1 and anti-PD-L1 therapy) in combination with standard of care doublet chemotherapy have shown a survival benefit, but overall outcomes remain poor.

Tisotumab has been shown to have better outcomes (PFS, OS and ORR) than single-agent chemotherapy in patients with recurrent or metastatic cervical cancer who failed doublet chemotherapy (paclitaxel + cisplatin, carboplatin or topotecan) + bevacizumab (if eligible) +/- pembrolizumab (for PD-L1-positive tumors), although AEs are common and lead to treatment interruption or discontinuation in a significant number of patients (especially ocular toxicity and peripheral neuropathy)

NCCN Guidelines for cervical cancer (Version 4.2025) recommend TV as a preferred second-line or subsequent therapy in patients with recurrent or metastatic cervical cancer after one of the regimens above.

VHA Oncology Cervical Cancer Clinical Pathway (v1.2025) directs to TV in the recurrent setting following prior systemic therapy and prior pembrolizumab.

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References

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2. Coleman R, Larusso D, Gennigens C, et al., 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. *Lancet Oncol* 2021;22:609-19.
3. Vergote I, van Neiuwenhuysen E, O'Cearbhaill R, et al., Tisotumab vedotin in combination with carboplatin, pembrolizumab or bevacizumab in recurrent or metastatic cervical cancer: Results from the innovaTV 205/GOG-3024/ENGOT-cx8 study. *J Clin Oncol* 2023;41:5536-49.
4. Vergote I, Gonzalez-Martin A, Fujiwara K, et al. Tisotumab vedotin as second or third-line therapy for recurrent cervical cancer. *N Engl J Med* 2024;391:44-55.
5. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 4.2025