Datopotamab deruxtecan-dlnk (DATROWAY)
National Drug Monograph
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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	A trophoblast cell surface antigen 2 (Trop-2)-directed antibody and topoisomerase I inhibitor (deruxtecan; DXd) conjugate.
Indication Under Review	- For the treatment of unresectable or metastatic, hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative (IHC 0, IHC 1+, or IHC 2+/ISH-) breast cancer after prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease. - For the treatment of locally advanced or metastatic epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) after prior EGFR-directed therapy and platinum-based chemotherapy. *Currently under accelerated approval based on objective response rate (ORR) and duration of response from the TROPION-Lung05 and TROPION-Lung01 trials.
Dosage Regimen	Datopotamab deruxtecan (Dato-DXd) 6 mg/kg (maximum 540mg) intravenously every 3 weeks until disease progression or unacceptable toxicity.
Dosage Forms Under Review	100 mg datopotamab deruxtecan as lyophilized powder in a single-dose vial.

EFFICACY CONSIDERATIONS

	UNRESECTABLE/METASTATIC, HR-POSITIVE, HER2-NEGATIVE BREAST CANCER
Trial	**TROPION-Breast01 (NCT05104866)[2]**
Design	Global, phase III, open-label, randomized study
Population	N=732; ≥18 years of age; inoperable or metastatic HR+/HER2- (IHC 0, IHC 1+, or IHC 2+/ISH-) breast cancer; 1-2 prior lines of chemotherapy in the inoperable/metastatic setting; ECOG PS 0-1; progression on or unsuitable for endocrine therapy Excluded: Metastases to the bone only; persistent toxicities from prior chemotherapy; history of interstitial lung disease (ILD)/pneumonitis requiring steroids or active ILD/pneumonitis; uncontrolled or significant cardiac disease; clinically significant corneal disease; prior treatment with topoisomerase I inhibitors, Trop-2-directed therapy, or same investigator choice chemotherapy (ICC)
Demographics	Median age 55 years (28-86); 99% female; 48% White; 41% Asian; median of 3 prior lines of anticancer therapy (including chemotherapy, hormonal therapy, immunotherapy, and targeted therapy); 57% ECOG PS 0; 97% visceral metastases
Intervention	Dato-Dxd 6 mg/kg IV every 3 weeks (n=365)
Comparator	Investigator choice chemotherapy (ICC; n=367) Eribulin 1.4 mg/m^2 IV days 1&8 every 3 weeks Capecitabine 1,000 or 1,250 mg/m^2 PO BID days 1-14 every 3 weeks Vinorelbine 25 mg/m^2 IV days 1&8 every 3 weeks Gemcitabine 1,000 mg/m^2 IV days 1&8 every 3 weeks
Results	Dato-DXd vs ICC (median follow-up 10.8 months) **Primary endpoint- PFS, median (months)**: 6.9 vs 4.9, HR 0.63 (95% CI, 0.52-0.76; p<0.0001) Time to first subsequent therapy, median (TFST; months): 8.2 vs 5, HR 0.53 (95% CI, 0.45-0.64) ORR (%): 36.4 vs 22.9, OR 1.95 (95% CI, 1.41-2.71) Duration of response, median (months): 6.7 vs 5.7 *Sustained PFS benefit across all subgroups *OS data not fully mature
	LOCALLY ADVANCED/METASTATIC, EGFR-MUTATED NSCLC
Trial	**TROPION-Lung05 (NCT04484142)[3]**
Design	Global, phase II, single-arm, open-label study
Population	N=137; ≥18 years of age; advanced or metastatic NSCLC with any actionable genomic alterations (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, *RET*); 1-2 prior lines of cytotoxic therapies (at least 1 platinum-containing regimen) and 1-2 prior lines of targeted therapies for actionable mutations; ECOG PS 0-1

		Excluded: History of interstitial lung disease (ILD)/pneumonitis requiring steroids or active ILD/pneumonitis; uncontrolled or significant cardiac disease; clinically significant corneal disease; prior treatment with topoisomerase I inhibitors or Trop-2-directed therapy; untreated or symptomatic CNS metastases; *KRAS* mutations without other abovementioned alterations
	Demographics	Median age 61 years (29-79); 60.6% female; 56.9% Asian; 31.4% White; *EGFR* mutations 56.9%; prior EGFR TKI 65% (osimertinib 44.5%); ECOG PS 1 67.2%
	Intervention	Dato-Dxd 6 mg/kg IV every 3 weeks (n=137)
	Results	**Primary endpoint- ORR (%)**: 35.8 (95% CI, 27.8-44.4) **43.6% in patients with *EGFR* mutations**; 23.5% in patients with *ALK* rearrangements 2.9% complete response (all 4 in *EGFR* mutations group); 32.8% partial response Duration of response, median (months): 7.0 (95% CI, 4.2-9.8) PFS, median (months): 5.4 (95% CI, 4.7-7.0) 5.4-8.3 months in patients with *EGFR* mutations; 2.6-6.9 months in patients with *ALK* rearrangements OS, median (months): 13.6 (95% CI, 9.9-NE)
	Trial	**TROPION-Lung01 (NCT04656652)[4]**
	Design	Global, open-label, randomized, phase III study
	Population	N=604; ≥18 years of age; stage IIIb/c or IV NSCLC; prior platinum-based chemotherapy and immunotherapy only (for patients without actionable genomic alterations), or 1-2 lines of targeted therapy and platinum-based chemotherapy +/- immunotherapy (for patients with *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET* alterations); ECOG PS 0-1 Excluded: Current/suspected ILD or history of ILD requiring steroids; uncontrolled or significant cardiac disease; clinically significant corneal disease; prior treatment with topoisomerase I inhibitors, Trop-2-directed therapy, or docetaxel; untreated or symptomatic CNS metastases
	Demographics	Dato-DXd vs Docetaxel Median age 63 vs 64 years (26-84 vs24-88); 61.2% vs 68.9% male; 41.1% vs 41.3% White; 39.8% vs 39.3% Asian; 16.7% actionable genomic alterations present (in both groups); ECOG PS 1 70.2% vs 69.2%
	Intervention	Dato-Dxd 6 mg/kg IV every 3 weeks (n=299)
	Comparator	Docetaxel 75 mg/m^2 IV every 3 weeks (n=305)
	Results	Dato-DXd vs Docetaxel (median follow-up 10.9 months) **Primary endpoints** **PFS, median (months)**: 4.4 vs 3.7, HR 0.75 (95% CI, 0.62-0.91; p=0.004) Nonsquamous histology: 5.5 vs 3.6, HR 0.63 (95% CI, 0.51-0.79) **Nonsquamous AND actionable genomic alterations: 5.7 vs 2.6, HR 0.35 (95% CI, 0.21-0.60)** Squamous histology: 2.8 vs 3.9, HR 1.41 (95% CI, 0.95-2.08) **OS, median (months)**: 12.9 vs 11.8, HR 0.94 (95% CI, 0.78-1.14; p=0.530) Nonsquamous histology: 14.6 vs 12.3, HR 0.84 (95% CI, 0.68-1.05) **Nonsquamous AND actionable genomic alterations: 15.6 vs 9.8, HR 0.65 (95% CI, 0.40-1.08)** Squamous histology: 7.6 vs 9.4, HR 1.32 (95% CI, 0.91-1.92) ORR (%): 26.4 vs 12.8; all four complete responses occurred in the Dato-DXd group Duration of response, median (months): 7.1 vs 5.6

SAFETY CONSIDERATIONS	**Boxed Warnings**	None
	Contraindications	None
	Other Warnings	Interstitial lung disease (ILD)/pneumonitis: Occurred in 7% patients with NSCLC (0.6% grade 3; 0.4% grade 4; 1.7% fatal) with median time to onset of 1.4 months (0.2-9). Occurred in 3.6% patients with breast cancer (0.7% grade 3; 0.2% fatal) with median time to onset of 2.8 months (1.1-10.8). Ocular adverse reactions: Occurred in 36% patients (2.2% grade 3; 0.1% grade 4) with median time to onset of 2.3 months (0.03-23.2). Most common ocular reactions were dry eye, keratitis, and increased lacrimation. Ophthalmic exam should be performed prior to treatment initiation, annually while on treatment, and at the end of treatment. Stomatitis: Occurred in 63% patients (8% grade 3; 0.1% grade 4) with median time to onset of 0.5 months (0.03-18.6). Embryo-fetal toxicity: Can cause fetal harm in a pregnant woman. Advise effective contraception.

Pre-medications	Pre-medications recommended to be given 30-60 minutes prior to each infusion: Diphenhydramine 25-50mg PO/IV or equivalent Acetaminophen 650-1,000mg PO/IV or equivalent 5-HT3 serotonin antagonist or other appropriate antiemetic PO/IV Recommended that patient hold ice chips in mouth throughout the duration of each infusion.
Supportive Care	Dato-DXd has a high-emetic risk; scheduled and as needed antiemetics are recommended. Throughout the duration of treatment, patients should administer the following medications: Preservative-free lubricant eye drops: both eyes at least four times daily Dexamethasone 0.1mg/mL oral solution (or equivalent): Swish/spit 10 mL four times daily
Adverse Events	≥20% (all grades): stomatitis, nausea, fatigue, alopecia, constipation, decreased appetite, rash, vomiting, musculoskeletal pain ≥2% laboratory abnormalities (grade 3-4): decreased lymphocytes, decreased hemoglobin
Drug Interactions	No clinically significant changes in pharmacokinetics of Dato-DXd found in clinical drug-interaction studies.

THERAPEUTIC ALTERNATIVES

UNRESECTABLE/METASTATIC, HR-POSITIVE, HER2-NEGATIVE BREAST CANCER

DRUG	VANF	CFU	OUTCOMES	CLINICAL GUIDELINES
Datopotamab deruxtecan	TBD	TBD	P3 trial (TROPION-Breast01[2]) N=365 ORR 36.4%; mPFS 6.9 mos Grade ≥3 TRAEs 20.8%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 2A); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 2A, preferred)
Fam-trastuzumab deruxtecan	PA-F	Yes	P3 trial (DESTINY-Breast06[6]) N=436 ORR 57.3%; mPFS 13.2 mos Grade ≥3 AEs 52.8%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 1, preferred) **VA Breast Cancer** Stage IV HR-positive/HER2-low; Triple-negative breast cancer
Sacituzumab govitecan	PA-F	No	P3 trial (TROPiCS-02[7]) N=272 ORR 21%; mPFS 5.5 mos Grade ≥3 TRAEs 74%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 1, preferred); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 1, preferred) **VA Breast Cancer** Stage IV HR-positive/HER2-negative; Triple-negative breast cancer
Capecitabine	PA-F	No	P2 trial[8] N=73 ORR 35.6%; mPFS mos Grade ≥3 AEs 26%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 2A); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 2A) **VA Breast Cancer** Stage IV HR-positive/HER2-negative; Triple-negative breast cancer
Gemcitabine	PA-F	No	Retrospective study[9] N=75 ORR 10.6%; mPFS 4.61 mos Grade ≥3 neutropenia 6.6%, thrombocytopenia 2.7%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 2A); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 2A) **VA Breast Cancer** Stage IV HR-positive/HER2-negative; Triple-negative breast cancer
Eribulin	PA-F	No	P3 trial (EMBRACE[10]) N=508 ORR 12%; mPFS 3.7 mos Serious AEs 25%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 2A); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 2A) **VA Breast Cancer**

				Stage IV HR-positive/HER2-negative; Triple-negative breast cancer
Vinorelbine	PA-F	No	P3 trial (GEICAM[11]) N=126 ORR 26%; mPFS 4.0 mos Grade ≥3 neutropenia 44%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 2A); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 2A) **VA Breast Cancer** Stage IV HR-positive/HER2-negative; Triple-negative breast cancer
Doxorubicin	PA-F	No	Prospective study[12] N=21 ORR 38.1%; mOS 11 mos	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 2A); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 2A) **VA Breast Cancer** Stage IV HR-positive/HER2-negative; Triple-negative breast cancer
Paclitaxel	PA-F	No	P2 trial[13] N=212 ORR 21.5%; mOS 12.8 mos Grade ≥3 neutropenia 15%	**NCCN Breast 2.2026**[5] Second line with visceral crisis or endocrine refractory disease (category 2A); First line for triple-negative disease with PD-L1 CPS <10 and no germline *BRCA* mutations (category 2A) **VA Breast Cancer** Stage IV HR-positive/HER2-negative; Triple-negative breast cancer
LOCALLY ADVANCED/METASTATIC, EGFR-MUTATED NSCLC				
DRUG	**VANF**	**CFU**	**OUTCOMES**	**CLINICAL GUIDELINES**
Datopotamab deruxtecan	TBD	TBD	P2 trial (TROPION-Lung05[3]) N=137 ORR 35.8%; mPFS 5.4 mos Grade ≥3 TRAEs 28.5% N=78 with *EGFR* alterations ORR 43.6%; 5.8 mos P3 trial (TROPION-Lung01[4]) N=299 ORR 26.4%; mPFS 4.4 mos Grade ≥3 TRAEs 25.6% N=48 nonsquamous with actionable genomic alterations ORR 37.5%; mPFS 5.7 mos	**NCCN NSCLC 5.2026**[14] Subsequent therapy for *EGFR* mutations/alterations (category 2A)
Osimertinib	PA-F	Yes	P2 trial (LAURA[15]) N=143 stage III NSCLC ORR 57%; mPFS 39.1 mos Grade ≥3 AEs 35% P3 trial (AURA3[16]) N=279 locally advanced/ metastatic NSCLC ORR 71%; mPFS 10.1 mos Grade ≥3 AEs 23%	**NCCN NSCLC 5.2026**[14] Subsequent therapy for *EGFR* mutations/alterations (category 2A) **VA Lung Cancer** *EGFR* mutation-positive, advanced NSCLC
Amivantamab	PA-F	Yes	P1 trial (CHRYSALIS[17]) N=114 ORR 40%; mPFS 8.3 mos Grade ≥3 AEs 35%	**NCCN NSCLC 5.2026**[14] Subsequent therapy for *EGFR* mutations/alterations (category 2A) **VA Lung Cancer** *EGFR* mutation-positive, advanced NSCLC
Amivantamab + lazertinib	NF	No	P1 trial[18] N=45	**NCCN NSCLC 5.2026**[14]

				ORR 36%; mPFS 4.9 mos Serious AEs 38%	Subsequent therapy for *EGFR* mutations/alterations (category 2A) **VA Lung Cancer** *EGFR* mutation-positive, advanced NSCLC
	Carboplatin + pemetrexed + amivantamab	PA-F	No	P3 trial (MARIPOSA-2[19]) N=131 ORR 64%; mPFS 6.3 mos Grade ≥3 AEs 72%	**NCCN NSCLC 5.2026**[14] Subsequent therapy for *EGFR* mutations/alterations (category 2A)

VHA PLACE IN THERAPY	**Potential Use in VHA**	1. Trophoblast cell surface antigen 2 (Trop-2) is a transmembrane glycoprotein encoded by the *TACSTD2* gene that functions as a calcium signal transducer leading to cell proliferation via various signaling cascades. Trop-2 expression has been found in a variety of cancers, primarily solid tumors.[20] 2. Trop-2 is not currently tested for through the VHA National Precision Oncology Program (NPOP); however, Trop-2 expression was not associated with difference in response in the TROPION-Lung05 study.[3] Trop-2 expression was not reported in either TROPION-Lung01 or TROPION-Breast01.[2,4]
	For breast cancer	3. Datopotamab deruxtecan was studied in inoperable or metastatic HR+/HER2- breast cancer. Median PFS was 6.9 months, compared to 4.9 months when given investigator choice chemotherapy. ORR was 36.4% and OS data is still maturing. Patients treated with Dato-DXd experienced less grade ≥3 treatment-related adverse events (trAEs), compared to the ICC group (20.8% vs. 44.7%); trAEs leading to dose reductions and discontinuations occurred in 20.8% and 2.5% of patients, respectively.[2] 4. Dato-DXd may serve as an effective option for inoperable or metastatic, HER2-negative breast cancer patients; however, the lack of mature OS data favors use of the previously approved antibody-drug conjugates (ADC; fam-trastuzumab deruxtecan and sacituzumab govitecan) and there is no data for Dato-DXd to be used after prior ADCs.
	For NSCLC	5. Datopotamab deruxtecan was studied in advanced or metastatic NSCLC with any actionable genomic alterations. ORR as 35.8% for the total population and 43.6% in patients with an EGFR mutation; all 4 complete responses occurred in patients with an EGFR mutation. Median PFS was 5.4 months and median OS was 13.6 months. 28.5% patients experienced a grade ≥3 trAE with 19.7% requiring dose reduction and 5.1% leading to discontinuation of Dato-DXd.[3] 6. Dato-DXd may serve the Veteran population as an effective option for EGFR-mutated, advanced or metastatic NSCLC. Given the limited options following systemic chemotherapy and EGFR tyrosine kinase inhibitors, Dato-DXd can fill the role for those with acquired resistance or otherwise failed prior lines of therapy.
	Overall	7. Multiple phase II-III trials are ongoing for the use of Dato-DXd in new indications, including triple-negative breast cancer and pan-tumor studies for various solid tumors. 8. Significant toxicity profile (risk of ILD/pneumonitis, ocular reactions, and stomatitis) should be considered in context of the Veteran and ensure appropriate pre-medications and monitoring are performed. Intensive supportive care is necessary for use of this drug.

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