Fam-trastuzumab deruxtecan-nxki (ENHERTU)
National Drug Monograph
June 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- **Fam-trastuzumab deruxtecan-nxki** (will be referred to **trastuzumab deruxtecan** for the remainder of the monograph) is an antibody-drug conjugate (ADC) composed of a HER2-directed monoclonal antibody and topoisomerase inhibitor.

Indication(s) Under Review in This Document

- Adults with unresectable or metastatic HER2-positive breast cancer who have received at least 2 prior anti-HER2 therapies in the metastatic setting (full approval)
- Adults with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen (full approval)

Dosage Form(s) Under Review

- ***Do NOT substitute trastuzumab deruxtecan for or with trastuzumab, trastuzumab biosimilars or ado-trastuzumab emtansine.***
    - Breast cancer dosage is 5.4 mg/kg IV once every 3 weeks
    - Gastric cancer dosage is 6.4 mg/kg IV once every 3 weeks

Clinical Evidence Summary

Efficacy Considerations

- FDA approval in breast cancer is supported by the study DESTINY-Breast03 (NCT03529110) while approval in gastric cancer is supported by DESTINY-Gastric01 (NCT03329690).
- Trastuzumab deruxtecan received accelerated approval in Dec. 2019 for treatment of unresectable or metastatic breast cancer in patients who have received at least 2 prior HER2-directed regimens. Full approval was received May 2022 based upon DESTINY-Breast03 and led to the change in indication to use after one prior anti-HER2-based regimen.

Efficacy in Breast Cancer

Study	Design/Population	Intervention	Efficacy Results
DESTINY-Breast01	Multicenter, single arm Female patients with HER2+*, unresectable and/or metastatic BrCa; s/p ≥ 2 prior anti-HER2 therapies Exclusions: clinically significant CV disease, active brain mets, ECOG PS > 1 *HER2+ defined as HER2 IHC 3+ or ISH+	Trastuzumab-deruxtecan 5.4 mg/kg IV every 3 weeks until PD or unacceptable toxicity Demographics: N=184 mAge 55 yrs (28-96) 76% < 65 yrs White 55%; Asian 38% ECOG PS 0 55%; 1 44% Visceral mets 92% Bone mets 29% Brain mets 13% Hormone Receptor+ 53% Med 6 prior treatments; Prior treatments: Trastuzumab 100% Tras-emtansine 100% Pertuzumab 66% Other anti-HER2 54%	Median follow-up 11 mos; ORR 60.3% (52.9-67.4) CR 4.3% PR 56% DoR 14.8 months mPFS 16.4 months (12.7-NR) 3L setting: Accelerated approval based on ORR and DoR.
DESTINY-Breast03 Cortes J, et. al. N Engl J Med 2022; 386: 1143-1154	Phase 3, MC, OL, RCT Patients with HER2+, mBC s/p trastuzumab and taxane Exclusions: symptomatic brain mets; rec'd prior HER2+ ADC for mBC, history ILD	Randomized 1:1 Tras-deruxtecan (n=261) vs. tras-emtansine (n=263) Demographics: mAge 54 yrs (20-83) Asian 58% European 20% HER2 3+ 89 vs. 88% Med prior tx: 1 vs. 2 1 prior: 50 vs. 47% 2 prior: 22 vs. 25% 3 prior 13 vs. 13% Prior trastuzumab 99.6 vs. 99.6% Prior pertuzumab 62 vs. 60%	Median follow-up 16.2 mo: Tras-deruxtecan vs. tras- emtansine mPFS: NR vs. 6.8 months 12-mo PFS: 75.8 vs. 34.1 mo [HR 0.28 (0.22-0.37); p<0.001] PFS point estimates for all subgroups favor tras-deruxtecan Survival@12-mos: 94 vs. 86% [HR 0.55 (0.36-0.86); p=0.007 did not meet prespecified cutoff for significance p<0.000265] ORR 80 vs. 34% CR 16 vs. 9%

Safety Considerations in Breast Cancer

<table>
<tr><th>Study</th><th>Safety Results</th></tr>
<tr><td>DESTINY-Breast01
Unresectable and/or mBrCa
3L setting</td><td>Pooled analysis of 234 pts; mDoT 7 months
SAEs 20%: ILD, pna, n/v, cellulitis, hypokalemia, intestinal obstruction
Fatalities 4.3%: ILD (2.6%), AKI, acute hepatic failure, pna, hemorrhagic shock
Most common AEs ≥ 20%: ↓WBC, ↓hgb, ↓ANC, ↓plts, ↑AST, ALT, N/V/C/D, fatigue, alopecia, anemia, cough

AE led discontinuation 9%: ILD 6%
AE led dose interruptions 33%: neutropenia, anemia, thrombocytopenia, fatigue
AE led dose reductions 18%: fatigue, nausea, neutropenia</td></tr>
<tr><td>DESTINY-Breast03
Cortes J, et. al.
N Engl J Med 2022; 386: 1143-1154</td><td>Median follow-up 16.2 mo:
Tras-deruxtecan (T-DXd) n=257 vs. tras-emtansine (T-DM1) n=261

<table>
<tr><th></th><th>T-DXd (any)</th><th>≥ Gr 3</th><th>T-DM1 (any)</th><th>≥ Gr 3</th></tr>
<tr><td>Drug-related events</td><td>98.1</td><td>45.1</td><td>86.6</td><td>39.8</td></tr>
<tr><td>Neutropenia</td><td>42.8</td><td>19.1</td><td>11.1</td><td>3.1</td></tr>
<tr><td>Nausea</td><td>72.8</td><td>6.6</td><td>27.6</td><td>0.4</td></tr>
<tr><td>Vomiting</td><td>44</td><td>1.6</td><td>5.7</td><td>0.4</td></tr>
<tr><td>Fatigue</td><td>44.7</td><td>5.1</td><td>29.5</td><td>0.8</td></tr>
<tr><td>Alopecia</td><td>36.2</td><td>0.4</td><td>2.3</td><td>0</td></tr>
<tr><td>ILD/pneumonitis</td><td>27</td><td>2</td><td>5</td><td>0</td></tr>
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Efficacy in Gastric or GEJ Adenocarcinoma

Study	Design/Population	Intervention	Efficacy Results
DESTINY-Gastric01 South Korea, Japan	Multicenter, open-label Adults with HER2+ (IHC 3+ or IHC 2+/ISH+) locally advanced or metastatic gastric or GEJ adenocarcinoma Progressive disease on ≥ 2 prior regimens including trastuzumab, 5-FU based and platinum-based chemotherapy Exclusions: history/current ILD, clinically significant CV disease, active brain mets, ECOG PS > 1	Randomized 2:1 Trastuzumab deruxtecan 6.4 mg IV every 3 weeks or physician's choice: • Irinotecan 150 mg/m2 IV every 2 weeks or • Paclitaxel 80 mg/m2 IV weekly Demographics N=126 vs. N=62 mAge 66 yrs (28-82) Male 76% Asian 100% ECOG PS 0: 49%; 1 51% Gastric 87% GEJ 13% Median 3 prior regimens	Median follow-up Trastuzumab deruxtecan vs. irinotecan or paclitaxel OS 12.5 vs. 8.4 months [HR 0.59(0.39-0.88); p=0.0097] PFS 5.6 vs. 3.5 months [HR 0.47(0.31-0.71)] ORR 51 vs. 7%; p<0.0001 DoR 11.3 vs. 3.9 mos

Safety Considerations in Gastric Cancer

Study	Safety Results
DESTINY-Gastric01 South Korea, Japan Gastric or GEJ 2L setting	Median follow-up Trastuzumab deruxtecan vs. irinotecan or paclitaxel Safety evaluated in 187 pts mDoT 4.6 vs. 2.8 mos (paclitaxel/irinotecan) SAEs 44%: ↓ appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, fever, tumor hemorrhage Fatalities 2.4%: DIC, intestinal perforation, pneumonia Most common AEs ≥ 20%: ↓WBC, ↓hgb, ↓ANC, ↓plts, ↑AST, ALT, N/V/C/D, fatigue, alopecia, anemia, cough, ↑ alk phos, ↑ Tbili, pyrexia AE led discontinuation 15%: due to ILD 6% AE led dose interruptions: neutropenia, anemia, ↓ appetite, leukopenia, ILD, pneumonia, thrombocytopenia, fatigue, upper RTI, diarrhea AE led dose reductions 32%: neutropenia, ↓ appetite, fatigue, nausea, febrile neutropenia

Overall Safety Considerations

- **Boxed warnings:**
  Interstitial lung disease (ILD) and pneumonitis have been reported and included fatal cases. Closely monitor for signs/symptoms that include cough, dyspnea, fever and other new or worsening respiratory symptoms. Permanently discontinue in patients with Grade 2 or higher ILD/pneumonitis. Advise patients of risk and to report symptoms immediately.
  Embryo-fetal harm can result if exposed during pregnancy. Advise patients of the risk and need for effective contraception.
- **Contraindications:** None
- **Other warnings / precautions**:
  Neutropenia. Monitor CBC at baseline, prior to each dose and as clinically indicated
  Left Ventricular Dysfunction. Evaluate LVEF at baseline and at regular intervals, as clinically indicated. Treatment interruption/discontinuation may be needed. Permanently discontinue in symptomatic CHF
  Moderately emetogenic. Ensure appropriate antiemetics are provided to prevent acute and delayed nausea/vomiting.

Other Therapeutic Options in Breast Cancer

Drug	Formulary status	Clinical Guidance for Therapeutic Alternatives in Breast Cancer	Other Considerations
Tras-deruxtecan T-DXd T-DXd 5.4 mg/kg IV every 3 weeks (breast)	TBD	2L: P3 evidence vs. tras-emtansine (DESTINY-Breast03); n=524 12-mos PFS 76 vs. 34%; ORR 83 vs. 36% NCCN v2.2022, preferred, category 1 3L: P2 evidence (DESTINY-Breast01) ORR 60% (CR 4.3%; PR 56%); DoR 11.3 mos	2L use, FDA approved OS data not yet mature; impressive PFS and ORR results Greater risk of ILD with tras-deruxtecan and more drug-related AEs overall
Tras-emtansine T-DM1 T-DM1 3.6 mg IV every 3 weeks	F	2L: P3 (TH3RESA) T-DM1 vs. clinician choice; n=602 PFS 6.2 vs. 3.3 mos [HR 0.53 (0.42-0.66)] OS 22.7 vs. 15.8 mos [HR 0.68 (0.54-0.85)] 2L: P3 (EMILIA) T-DM1 vs. lapatinib/capecitabine; n=978 PFS 10 vs. 6 mos [HR 0.65 (0.55-0.77)]; OS 31 vs. 25 mos [HR 0.68 (0.55-0.85)] NCCN v2.2022, other recommended regimen, cat 2A UpToDate: T-DM1 preferred if PD on prior HER2-tx	2L use FDA approved
Tucatinib Tucatinib 300 mg PO twice daily + trastuzumab + capecitabine	NF	3L: P3, heavily pre-treated HER2+ mBrCa (med 4 prior) Tucatinib/tras/capecitabine vs. tras/capecitabine 12-mos PFS 33 vs. 12% mPFS 7.8 vs. 5.6 mos; 2-yr OS 45 vs. 27% 1-yr PFS 25 vs. 0% among those with brain mets NCCN v2.2022, other recommended regimen, cat 1 UpToDate:	3L and beyond; FDA approved Crosses BBB, often reserved for later-lines, esp if brain mets Oral formulation, given with trastuzumab and capecitabine
Margetuximab Margetuximab 15 mg/kg IV every 3 wks + chemo	NF	3L: P3 (SOPHIA) margetuximab/chemo vs. tras/chemo mPFS 5.8 vs. 4.9 mos NCCN v2.2022, other recommended regimen, cat 2A UpToDate: modest benefit, reserved after all other options failed	3L in combination with chemo; Modest improvement in PFS

Other Considerations in Breast Cancer

Risk-Benefit Assessment in breast cancer

- **Outcome in clinically significant area:** PFS, OS data not yet mature
- **Effect Size:** HR 0.28 (0.22-0.37); p< 0.001
- **Potential Harms:** Drug-Related Events 98% (gr 3 45%); ILD 27%
- **Net Clinical Benefit:** benefit moderate-high with toxicity

Other Therapeutic Options in Gastric or GEJ Adenocarcinoma

Drug	Formulary status	Clinical Guidance for Therapeutic Alternatives in Gastric Cancer	Other Considerations
Tras-deruxtecan T-DXd T-DXd 6.4 mg/kg IV every 3 weeks (gastric)	TBD	P2, DESTINY-Gastric01 trial; n=187 s/p 2 prior therapies, including trastuzumab Randomized T-DXd vs. MD choice (irinotecan or paclitaxel) ORR 51 vs. 14%; p<0.001 mOS 12.5 vs. 8.4 mos; HR 0.59; 0.39-0.88; p=0.01 mPFS 5.6 vs. 3.5 mos; HR 0.47; 0.31-0.71 NCCN v2.2022 T-DXd preferred 2L for HER2+ adenocarcinoma	SAE's neutropenia 51%, anemia 38%, thrombocytopenia 10%, ILD 10%
Paclitaxel + ramucirumab	PA-F (h/o) PA-F w/CFU	P3, RAINBOW trial; n=665 Previously treated Randomized to 2L paclitaxel + ramucirumab or PBO mOS 9.6 vs. 7.4 mos; HR 0.80; 0.68-0.96 PFS 4.4 vs. 2.9 mos; ORR 28 vs. 16% CFU: 2L in advanced/metastatic disease	Gr 3 neutropenia (41 vs. 19%); Gr 3 HTN (14 vs. 2%) HER2 expression not identified; Not anti-HER2-directed therapy
Tras-emtansine T-DM1 T-DM1 3.6 mg IV every 3 weeks	PA-F w/CFU	P2/3, GATSBY trial; n=335 Patients randomized to 2L T-DM1 vs. taxane mOS 7.9 vs. 8.6 mos; HR 1.15; 0.87-1.51; p=0.86 No benefit noted in 2L	
Trastuzumab	PA-F w/CFU	P2, T-ACT trial; n=91 Patients refractory to trastuzumab + fluoropyrimidine/platinum Randomized to 2L paclitaxel with or without trastuzumab No benefit to continuing trastuzumab 2L 69% lost HER2+ after progression	
Lapatinib	NF	P3, TyTAN trial; n=261 Patients randomized to paclitaxel with/without lapatinib No benefit in OS (11 vs. 8.9 mos); PFS (5.4 vs. 4.4 mos) Not all received trastuzumab as 1L (7 vs. 15%)	

Other Considerations in Gastric Cancer

Risk-Benefit Assessment in gastric cancer

- **Outcome in clinically significant area:** mOS
- **Effect Size:** HR 0.59; 0.39-0.88; p=0.01
- **Potential Harms (AEs > 20%):** ↓WBC, ↓hgb, ↓ANC, ↓plts, ↑AST, ALT, N/V/C/D, fatigue, alopecia, anemia, cough, ↑ alk phos, ↑ Tbili, pyrexia
- **Net Clinical Benefit:** significant, with toxicity

Projected Place in Therapy

- Breast cancer is the second leading cause of death in women; in the US, it is estimated to cause 40,000 deaths annually. Male breast cancer is less common with an estimated 2600 cases diagnosed each year.
- An estimated 15-20% of patients with metastatic breast cancer (MBC) can be characterized by overexpressed or amplified human epidermal growth factor receptor 2 (HER2). HER2-positive disease is typically more aggressive and affects a younger population.
- 5-year survival rates of HER2-positive MBC range from 40-45%.
- Standard 1L for HER2-positive MBC consists of anti-HER2-directed antibodies, trastuzumab and pertuzumab, with a taxane; 2L therapy consists of the antibody drug conjugate T-DM1 (trastuzumab emtansine).
- T-DXd has been a 3L option in the advanced HER2+ breast cancer setting since its approval in 2019 after patients have received 2 prior anti-HER2-directed regimens.
- Recent P3 data comparing T-DXd to T-DM1 has shown improved PFS and ORR in the 2L setting.
    - OS data is not yet mature; longer follow up is needed to determine potential OS benefit
- Long-term toxicities of T-DXd are not known. Toxicities, primarily ILD/pneumonitis, may limit its use and should be considered for select patients.
- Overexpression or amplification of HER2 in gastric or GEJ adenocarcinoma, similarly, affects ~20% of those with advanced disease. Chemotherapy plus trastuzumab is the standard 1L recommendation.
- Until now, no other HER2-directed therapies have shown benefit in patients who have received a prior 1L trastuzumab-based regimen. Close monitoring is needed for new or worsening respiratory symptoms, signs of left ventricular dysfunction and risk of myelosuppression.

Addendum (June 17, 2022)

- Results from DESTINY-Breast04 were presented at the ASCO Plenary Session on 6/6/2022, which coincided with the release of the N Engl J Med article (doi: 10.1056/NEJMoa2203690), entitled *Trastuzumab Deruxtecan in Previously Treated HER2-low Advanced Breast Cancer*. This was a Phase 3, randomized, 2-group, open-label trial that included patients with HER2-low unresectable or MBC s/p chemo for MBC or with progressive disease within 6 months of adjuvant chemotherapy; if patients were HR+, they must have received at least 1L endocrine therapy. HER2-low was defined as 1+ IHC or 2+ IHC and ISH-negative
- Patients were randomized 2:1 to trastuzumab deruxtecan vs. physician's choice of capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel
- At a median follow up of 18.4 months, the primary endpoint of PFS in HR+ patients showed a mPFS 10.1 vs. 5.4 months [HR 0.51; 95% CI 0.40-0.64; p< 0.001]; among all patients (HR+ and HR-) mPFS 9.9 vs. 5.3 months [HR 0.50; 95% CI 0.40-0.63; p< 0.001] and among HR- patients, mPFS 8.5 vs. 2.9 months [HR 0.46; 95% CI 0.24-0.89]. mOS of all patients was 23.4 vs. 16.8 mos [HR 0.64; 95% CI 0.49-0.84; p=0.001]
- Of note, a greater incidence of toxicities were noted in the trastuzumab-deruxtecan arm and warrant consideration. In light of this new and practice-changing information, the additional indication in HER2-low MBC, as defined per DESTINY-Breast04, should be considered in appropriate populations.

References

1. Modi S, et al for the DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020: 382: 610.

2. Cortes, J et al. for the DESTINY-Breast03 Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 2022; 386: 1143.

3. Murthy RK, et al. Tucatinib, trastuzumab and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2020; 382: 597.

4. Rugo HS, et al for the SOPHIA Study Group. Efficacy of margetuximab vs. trastuzumab in patients with pretreated ERBB@-positive advanced breast cancer: a phase 3 randomized clinical trial. JAMA Oncol 2021; 7: 573.

5. Verma S, et al. for the EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367: 1783.

6. Shitara K, et al. for the DESTINY-Gastric01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020; 382: 2419.

7. Makiyama A, et al. Randomized, Phase II Study of Trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT study). J Clin Oncol 2020; 38: 1919.

8. Satoh T, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN-a randomized, phase III study. J Clin Oncol 2014; 32: 2039.

9. Thuss-Patience PC, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma (GATSBY): an international randomized, open-label, adaptive, phase 2/3 study. Lancet Oncol 2017; 18: 640.

10. Wilke H for the RAINBOW study group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-esophageal junction adenocarcinoma: a double-blind, randomized phase 3 trial. Lancet Oncol 2014; 15: 1224.

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