BC Cancer Protocol Summary for Second-Line Treatment of Metastatic or Locally Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma using Trastuzumab Deruxtecan (ENHERTU)

Protocol Code	*GIGAVENH*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Metastatic or locally advanced (unresectable) gastric, gastroesophageal junction (GEJ) or esophageal adenocarcinoma, and
- HER-2 positive/overexpression defined as either IHC3+, or FISH amplification ratio of greater than or equal to 2 per BC Cancer central laboratory, and
- Received a prior trastuzumab-based regimen in the first-line advanced treatment setting.

Patients should have:

- Good performance status,
- No signs or symptoms of cardiac disease. For patients with equivocal cardiac status, a MUGA scan or ECHO should be done and reveal a normal left ventricular ejection fraction.

Notes:

- Patients who started on second or later lines of treatment prior to October 1, 2025, and have not had previous treatment with trastuzumab deruxtecan (ENHERTU), may switch to GIGAVENH, provided:
  - all other eligibility criteria are met,
  - do not have to be progressing on current treatment to switch (patients who switch from other treatments to GIGAVENH may return to their previous treatment upon progression of GIGAVENH if clinically appropriate), and
  - switch occurs by March 31st, 2026.

EXCLUSIONS:

Patients must not have:

- Symptomatic spinal cord compression,
- Active untreated central nervous system metastases (unless asymptomatic and/or stable), or
- Current interstitial lung disease or pneumonitis

TESTS:

- Baseline: CBC & Diff, creatinine, total bilirubin, ALT
- Baseline if clinically indicated: CEA, CA 19-9, GGT, echocardiogram or MUGA scan for left ventricular ejection fraction (LVEF) assessment
- Prior to each dose: CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated: CEA, CA 19-9, alkaline phosphatase, sodium, potassium, magnesium, calcium, albumin, phosphate, echocardiogram or MUGA scan for LVEF assessment every 12 weeks, serum HCG, urine HCG

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy protocols (see protocol SCNAUSEA)

There is a risk of medication errors between trastuzumab deruxtecan (ENHERTU), trastuzumab (HERCEPTIN/funded biosimilar), and trastuzumab emtansine (KADCYLA). To minimize the risk, check the vial labels to ensure that the drug being prepared and administered is trastuzumab deruxtecan (ENHERTU).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
trastuzumab deruxtecan (ENHERTU)	6.4 mg/kg	IV in 100 mL D5W over 1 hour 30 min using a 0.2 micron in-line filter. Observe for 1 hour 30 min post-infusion. If no infusion reaction observed in Cycle 1, give subsequent doses over 30 min, observe for 30 min post-infusion. Observation period not required after 3 treatments with no reaction.

Repeat every 3 weeks until disease progression or unacceptable toxicity.

Dose Levels*

Starting Dose	Dose Level -1	Dose Level -2
6.4 mg/kg	5.4 mg/kg	4.4 mg/kg

* Dose should not be re-escalated after a dose reduction has been made

DOSE MODIFICATIONS:

1. Hematological

ANC ($\times 10^9$/L)		Platelets ($\times 10^9$/L)	Dose
Greater than or equal to 1.0	and	Greater than or equal to 75*	100%
0.5 to 0.99	or	25 to 74	Delay until ANC 1.0 and platelets 75 or greater, then maintain dose
Less than 0.5	or	Less than 25	Delay until ANC 1.0 and platelets 75 or greater, then reduce dose by one level
Febrile Neutropenia (ANC less than 1.0 and temperature greater than 38.3°C or sustained temperature of 38°C or greater for more than one hour)	and	Any	Delay until fever resolved and ANC 1.0 and platelets 75 or greater, then reduce by one dose level

*Although trials and product monograph used 50, given the risks of bleeding with GE cancers the threshold was raised to 75. Treatment below 75 is left to physician discretion.

2. Interstitial Lung Disease (ILD) or Pneumonitis

- Initiate corticosteroids immediately for symptomatic ILD/pneumonitis and continue for minimum 14 days before tapering over at least 4 weeks for patients with Grade 2 or higher ILD/pneumonitis, for Grade 1 with extensive lung involvement on imaging, or those at risk for progression of ILD/pneumonitis.

ILD or Pneumonitis	Management
Asymptomatic. Grade 1 (Clinical or diagnostic observations only, intervention not indicated)	▪ Delay until resolved to Grade 0, then: ○ if resolved in 28 days or less, maintain dose. ○ if resolution takes longer than 28 days, reduce by one dose level ▪ Consider corticosteroid treatment (e.g. predniSONE >0.5 mg/kg/day or equivalent
Symptomatic. Grade 2 or greater.	▪ Permanently discontinue trastuzumab deruxtecan (ENHERTU) ▪ Immediately initiate corticosteroid treatment (e.g. ≥1 mg/kg/day predniSONE or equivalent)

3. Left Ventricular Ejection Fraction (LVEF) Decreased

LVEF		LVEF Change from Baseline	Management
Greater than 45%	and	Absolute decrease from baseline 10 to 20%	Continue trastuzumab deruxtecan (ENHERTU)
40% to 45%	and	Absolute decrease from baseline less than 10%	▪ Continue trastuzumab deruxtecan (ENHERTU) ▪ Refer to cardiologist/cardio-oncologist for opinion ▪ Repeat LVEF assessment within 3 weeks.
	and	Absolute decrease from baseline 10 to 20%	▪ Delay trastuzumab deruxtecan (ENHERTU) ▪ Refer to cardiologist/cardio-oncologist for opinion ▪ Repeat LVEF assessment within 3 weeks. ▪ If LVEF not recovered to within 10% of baseline, permanently discontinue. ▪ If LVEF recovers to within 10% of baseline, resume at same dose.
Less than 40%	or	Absolute decrease from baseline greater than 20%	▪ Delay trastuzumab deruxtecan (ENHERTU) ▪ Refer to cardiologist/cardio-oncologist for opinion ▪ Repeat LVEF assessment within 3 weeks. ▪ If LVEF less than 40% or if absolute decrease from baseline greater than 20%, permanently discontinue
Symptomatic congestive heart failure			Permanently discontinue

PRECAUTIONS:

1. **Neutropenia**, including febrile neutropenia, is reported during treatment with trastuzumab deruxtecan (ENHERTU). Fever or other evidence of infection must be assessed promptly and treated aggressively.

2. **Infusion-Related Reactions (IRRs)** occurs rarely (1 to 3% of patients). Symptoms may include chills, shaking, shortness of breath, wheezing, itching, rash, hives, flushing, dizziness, or fever. Patients should be monitored for IRRs. See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Systemic Therapy Agents (SCDRUGRX).
3. **Interstitial lung disease (ILD)/pneumonitis** including fatal cases have been reported during treatment with trastuzumab deruxtecan (ENHERTU). Moderate renal impairment may increase risk. Monitor patients and immediately investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Treatment should be permanently discontinued in patients who are diagnosed with interstitial lung disease and drug induced pneumonitis. Treat with corticosteroids per dose modifications, above.
4. **Decreased left ventricular ejection fraction and left ventricular dysfunction:** Use caution in patients with a history of cardiac disease or LVEF less than 50%. Decreased LVEF and left ventricular dysfunction have been reported during treatment with trastuzumab deruxtecan (ENHERTU). Some patients may be asymptomatic. Permanent discontinuation may be necessary. See dose modifications, above.
5. **Renal Impairment:** No initial dose adjustment required for patients with mild or moderate renal impairment at baseline. Patients with moderate renal impairment may be at increased risk of adverse events including ILD and pneumonitis; monitor closely.
6. **Hepatic Impairment:** No initial dose adjustment required for mild or moderate hepatic impairment at baseline. Exposure may be increased in moderate hepatic impairment; monitor closely for toxicities.

Contact the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Shitara K, Bang YJ, Iwasa S, et al; DESTINY-Gastric01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020 Jun 18;382(25):2419-2430.
2. Van Cutsem E, di Bartolomeo M, Smyth E, et al; Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. Lancet Oncol. 2023 Jul;24(7):744-756.
3. Yamaguchi K, Bang YJ, Iwasa S et al; Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2–positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: Final overall survival (OS) results from a randomized, multicenter, open-label, phase 2 study (DESTINY-Gastric01). Journal of Clinical Oncology 2022 40:4_suppl, 242-242.
4. Trastuzumab Deruxtecan (Enhertu) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies April 2025; 5(4):1-29.