BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab Deruxtecan (ENHERTU)

Protocol Code	*BRAVENH*
Tumour Group	*Breast*
Contact Physician	*Dr. Nathalie LeVasseur*

ELIGIBILITY:

Patients must have:

Unresectable or metastatic breast cancer and one of the following indications:

1. HER2-positive disease
   - HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 at a quality assured laboratory, and
     - Previously treated with at least 1 prior regimen containing trastuzumab plus chemotherapy in the advanced setting, or
     - Relapsed on or within 6 months of neoadjuvant or adjuvant trastuzumab-based protocol,

OR

2. HER2-low disease
   - HER2-low (defined as IHC 1+ or IHC 2+ and FISH negative), and
   - Previously treated with at least 1 prior chemotherapy regimen in the advanced setting, or recurrence of cancer during or within 6 months of completing neoadjuvant or adjuvant chemotherapy, and
     - Hormone receptor negative patients*: no prior antibody-drug conjugate (i.e., no prior sacituzumab govitecan), or
     - Hormone receptor positive** patients: previously treated with at least 1 endocrine therapy (in adjuvant or advanced setting) and no longer considered candidate for further endocrine treatment per provider discretion

     * Patients with low ER expression (1 to 10 % of ER positive cells) may be treated as hormone receptor negative per physician discretion, and do not require prior endocrine therapy to be eligible for BRAVENH if other criteria are met

     ** Hormone receptor positive defined as:
     ER positive:
     - ER Allred score 3 to 8, with
     - Intensity: moderate or strong, and
     - More than 10% of ER positive cells and

     Regardless of PR results

Patients should have:

- ECOG status 0 to 2,
- 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.

Note: Patients with HER2-low disease are eligible for trastuzumab deruxtecan (BRAVENH) or sacituzumab govitecan (BRAVSG), but not sequential use of these agents. Switching for intolerance or toxicity is permitted.

EXCLUSIONS:

Patients must not have:

- Prior progression on trastuzumab emtansine for HER2-positive disease in the metastatic setting (KADCYLA per BRAVKAD). May use for intolerance to BRAVKAD,
- Relapsed on or within 12 months of adjuvant trastuzumab emtansine for HER2-positive disease (KADCYLA per UBRAJKAD),
- This drug used in combination treatment. This treatment is monotherapy,
- Current pregnancy or lactation,
- Symptomatic spinal cord compression,
- Active untreated central nervous system metastases (unless asymptomatic and/or stable),
- Current interstitial lung disease or pneumonitis

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, total bilirubin, ALT, pregnancy test prior to treatment in females of childbearing potential, CT chest
- Baseline if clinically indicated: GGT, LDH, alkaline phosphatase, CA 15-3, echocardiogram or MUGA scan for left ventricular ejection fraction (LVEF) assessment
- Prior each dose: CBC & Diff, platelets, creatinine, total bilirubin, ALT
- If clinically indicated: CA15-3, alkaline phosphatase, sodium, potassium, magnesium, calcium, albumin, phosphate, CT chest, echocardiogram or MUGA scan for LVEF assessment every 12 weeks, and pregnancy test in females of childbearing potential

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)	5.4 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 21 days. Continue until disease progression or unacceptable toxicity.

Dose Levels*

Starting Dose	Dose level -1	Dose level -2
5.4 mg/kg	4.4 mg/kg	3.2 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	50 to 74	Delay until ANC 1.0 and platelets 75, then 100%
0.5 or greater	and	25 to 49	Delay until ANC 1.0 and platelets 75. ▪ If recovered in 7 days or less, maintain dose level. ▪ If recovery takes more than 7 days, reduce dose by one level
Less than 0.5	or	Less than 25	Delay until ANC 1.0 and platelets 75, 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, then reduce by one dose level

2. Interstitial Lung Disease (ILD) or Pneumonitis

- Corticosteroids should be initiated immediately for symptomatic ILD/pneumonitis. Consider corticosteroids for suspected ILD/pneumonitis.
- Corticosteroid treatment should continue for minimum 14 days before tapering over at least 4 weeks for patients with Grade 2 or higher ILD/pneumonitis, or 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 if ILD/pneumonitis suspected (e.g. predniSONE ≥ 0.5 mg/kg/day or equivalent
Symptomatic. Grade 2 or greater.	▪ Permanently discontinue trastuzumab deruxtecan (ENHERTU) ▪ Immediately initiate corticosteroid treatment if ILD/pneumonitis suspected (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.

Call Dr. Nathalie LeVasseur or tumour group delegate at (604) 930-2098 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Cortés J, Kim SB, Chung WP, et al; DESTINY-Breast03 Trial Investigators. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med. 2022 Mar 24;386 (12):1143-1154.
2. CADTH: Trastuzumab Deruxtecan (Enhertu) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies Oct 2022; 2(10):1-17.
3. Modi S, Jacot W, Yamashita T, et al; DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20.
4. CADTH: Trastuzumab Deruxtecan (Enhertu) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies July 2023; 3(7):1-19.