BC Cancer Protocol Summary for Adjuvant Therapy for Breast Cancer using Trastuzumab Emtansine (KADCYLA)

Protocol Code	***UBRAJKAD***
Tumour Group	***Breast***
Contact Physician	***Dr Stephen Chia***

ELIGIBILITY:

Patient must have:
- HER2 positive early stage breast cancer with residual invasive disease in breast or axillary nodes after neoadjuvant treatment
  - HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 at a quality assured laboratory
- Prior neoadjuvant treatment which must include:
  - Minimum 6 cycles of chemotherapy with at least 9 weeks of taxanes and 9 weeks of trastuzumab (3 cycles of taxane and trastuzumab)
- Completed breast and axillary surgery with no clinically evident metastatic disease
- BC Cancer "Compassionate Access Program" request approval prior to treatment.

Note:
- Trastuzumab emtansine (KADCYLA) should start within 12 weeks of completion of surgery.
- Patients can be treated with up to 14 maximum cycles of trastuzumab emtansine, regardless of number of prior neo/adjuvant trastuzumab treatments assuming all other eligibility criteria are met
- If patients discontinue trastuzumab emtansine (KADCYLA) due to side effects, they can receive trastuzumab (BRAJTR)

Patients should have:
- ECOG status 0 or 1
- LVEF greater than or equal to 50%* prior to neoadjuvant trastuzumab
  * If LVEF at 45-50%, oncologist may decide to treat based on clinical assessment
- Adequate hematological, renal and hepatic function

EXCLUSIONS:
- Clinical T1aN0 or T1bN0 at presentation prior to neoadjuvant treatment
- Significant cardiovascular disease and/or LVEF less than 50%; if initial reading is less than 50%, physician may consider repeating for validity, or assessing LVEF by the other modality (e.g., echocardiogram instead of MUGA)
- Greater than or equal to grade 2 sensory or motor neuropathy
- Pregnancy or lactation

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, ALT, alkaline phosphatase, LDH, GGT, serum creatinine
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab emtansine (KADCYLA) and every 3-4 months during the treatment per the discretion of the treating physician. The maximum time between cardiac monitoring should be 4 months (see dose modification #3 for adjustment of trastuzumab emtansine (KADCYLA) based on changes in LVEF)
- Prior to each cycle: CBC & diff, platelets, bilirubin, ALT, alkaline phosphatase, LDH, GGT
- If clinically indicated: total protein, albumin, sodium, potassium, bilirubin, ALT, alkaline phosphatase, LDH, GGT, BUN, serum creatinine, ECG

PREMEDICATION:

- Antiemetic protocol for low emetogenic chemotherapy (see protocol SCNAUSEA)

There is a risk of medication errors between trastuzumab emtansine (KADCYLA) and trastuzumab (HERCEPTIN/HERZUMA). In order to minimize the risk, check the vial labels to ensure that the drug being prepared and administered is trastuzumab emtansine (KADCYLA).

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
trastuzumab emtansine (KADCYLA)	3.6 mg/kg	IV in NS 250 mL over 1 hour 30 minutes using a 0.2 micron in-line filter Observe for 1 hour 30 min post-infusion If no infusion reaction observed in Cycle 1, may give subsequent doses over 30 minutes, observe for 30 minutes post-infusion.

- Repeat every 21 days up to 14 cycles maximum

*Dose Levels

Starting Dose	Dose level -1	Dose level -2	Dose level -3
3.6 mg/kg	3 mg/kg	2.4 mg/kg	discontinue

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

If a planned dose is missed, it should be administered as soon as possible as per the physician's discretion. Do not wait until the next planned cycle if clinically appropriate.

DOSE MODIFICATIONS:

1. Hematological

- patients with platelets less than 100 x 10^9/L and patients on anti-coagulant treatment should be monitored closely while on treatment

Platelets x 10^9/L		ANC x 10^9/L	Dose
greater than or equal to 75	and	greater than or equal to 1	treat at same dose level as previous cycle
25 to 74	or	0.5 to 0.99	delay until platelet count recovers to greater than or equal to 75* (grade 1 or better) and ANC greater than or equal to 1, then treat at same dose level
less than 25	or	less than 0.5	delay until platelet count recovers to greater than or equal to 75* (grade 1 or better) and ANC greater than or equal to 1, then reduce one dose level

*permanently discontinue treatment if platelet count does not recover to greater than or equal to 75 or baseline within 42 days of last dose

2. Hepatic Impairment

- discontinue treatment in patients with serum transaminases greater than 3 x ULN and concomitant total bilirubin greater than 2 x ULN
- discontinue treatment in patient diagnosed with nodular regenerative hyperplasia

Increased Transaminases

Grade	ALT or AST	Dose
1	less than or equal to 2.5 x ULN	no dose adjustment
2	greater than 2.5 to less than or equal to 5 x ULN	continue treatment at same dose level
3	greater than 5 to less than or equal to 20 x ULN	delay until ALT or AST recovers to less than or equal to grade 2, then reduce one dose level
4	greater than 20 x ULN	discontinue treatment

Hyperbilirubinemia

Grade	bilirubin	Dose
1	less than or equal to 1.5 x ULN	no dose adjustment
2	greater than 1.5 to less than or equal to 3 x ULN	delay until total bilirubin recovers to grade 1 or better, then treat at same dose level
3	greater than 3 to less than 10 x ULN	delay until total bilirubin recovers to grade 1 or better, then reduce one dose level
4	greater than 10 x ULN	discontinue treatment

3. Cardiac

LVEF	Dose
greater than 45%	no dose adjustment
40% to less than or equal to 45% and decrease is within 10% points from baseline	continue treatment, repeat LVEF assessment within 3 weeks
less than 40%	Hold treatment, repeat LVEF assessment within 3 weeks. If LVEF less than 40% is confirmed, discontinue treatment
Symptomatic CHF	discontinue treatment

4. Peripheral Neuropathy

Patients (22%) receiving trastuzumab emtansine(KADCYLA) have reported peripheral neuropathy. Hold treatment in patients with grade 3 or 4 peripheral neuropathy until improvement to less than or equal to grade 2 and consider dose reduction when restarting. If grade 4 peripheral neuropathy consider risk benefit of continuing trastuzumab emtansine.

5. Renal Dysfunction

Creatinine Clearance (mL/min)	
greater than or equal to 30	no dose adjustment
less than 30	no data

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. Use with caution in patients who experience dyspnea at rest due to complications of advanced malignancy and co-morbidities; may be at an increased risk of developing interstitial lung disease (ILD), including pneumonitis. Trastuzumab emtansine (KADCYLA) should be permanent discontinued in patients who are diagnosed with **interstitial lung disease** and **drug induced pneumonitis**.
3. The DM1 moiety of trastuzumab emtansine (KADCYLA) is a substrate of **CYP 3A4**. Strong CYP 3A4 inhibitors may increase DM1 plasma levels and hence, its toxicity; therefore concurrent use should be avoided if possible. If concurrent use is unavoidable, consider delaying trastuzumab emtansine (KADCYLA) treatment until the strong CYP 3A4 inhibitor has been cleared from the system (approximately three half-lives of the inhibitor). Monitor patient for adverse reactions related to trastuzumab emtansine (KADCYLA).

Call Dr. Stephen Chia or tumour group delegate at (604) 877-6000 or 1-888-563-7773 with any problems or questions regarding this treatment program.

References:

Von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2 positive breast cancer. N Engl J Med 2019;380:617-28.