BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab Emtansine (KADCYLA)

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

ELIGIBILITY:

- Treatment of HER2-positive unresectable locally advanced or metastatic breast cancer patients who have received prior treatment with trastuzumab plus chemotherapy in the metastatic setting or have disease recurrence during or within 6 months of completing adjuvant therapy with trastuzumab plus chemotherapy.
- Patients who were started or had completed at least two lines of anti-HER 2 therapy for HER2-positive unresectable locally advanced or metastatic breast cancer **prior to 1 May 2014** are also eligible for trastuzumab emtansine (KADCYLA)
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 at a quality assured laboratory
- ECOG status 0 or 1
- Life expectancy of 3 months or more
- Adequate hematological, renal and hepatic function
- 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.
- A BCCA "Compassionate Access Program" or "Undesignated Indication" request with appropriate clinical information for each patient must be approved prior to treatment **Note:** only one anti-HER2 therapy will be funded in the second line setting (UBRAVKAD, UBRAVTCAP or UBRAVLCAP), no funding currently for third line anti-HER2 therapy.

EXCLUSIONS:

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Greater than or equal to grade 2 sensory or motor neuropathy
- ECOG 2-4
- Pregnancy or lactation
- Significant hepatic dysfunction

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, LFTs, serum creatinine
- Prior to Day 1 treatment: CBC & diff, platelets, bilirubin, LFTs
- If clinically indicated: MUGA scan or echocardiogram at baseline, and every 12 weeks during treatment is recommended but not mandatory
- If clinically indicated: any abnormal values

PREMEDICATION:

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

There is a risk of medication errors between trastuzumab emtansine (KADCYLA) and trastuzumab (HERCEPTIN). 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*	BCCA Administration Guideline
trastuzumab emtansine (KADCYLA)	3.6 mg/kg	IV in NS 250 mL (use in-line filter) over 1 hour 30 minutes 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. Continue until disease progression, no evidence of further clinical benefit or unacceptable toxicity.

*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	AST/ALT	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 AST/ALT 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.

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.

Date activated: 1 May 2014

Date revised: 1 Apr 2015 (cardiac monitoring clarified)

References:

Verma S, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367(19):1783-91.