BC Cancer Protocol Summary for Therapy for Metastatic Breast Cancer using Capecitabine and Lapatinib

Protocol Code	*BRAVLCAP*
Tumour Group	*Breast*
Contact Physician	*Dr. Stephen Chia*

ELIGIBILITY:

- advanced breast cancer patients with HER-2 expressing breast cancer whose cancer has progressed on one prior therapy with trastuzumab-based protocol in the advanced setting (BRAVTRAD, BRAVTRAP, BRAVTPCARB, BRAVPTRAD, BRAVTRVIN) or who has relapsed on or within 12 months of adjuvant trastuzumab
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- Patient ineligible for, or unwilling to participate in, a clinical trial or no suitable clinical trial available
- Life expectancy greater than 3 months
- 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.
- Patient must be able to report any severe toxicity such as diarrhea, hand/foot syndrome, severe nausea, stomatitis
- **Note:** only one anti-HER2 therapy will be funded in the second line setting (UBRAVKAD, BRAVTCAP or BRAVLCAP), 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)
- severe renal impairment (calculated creatinine clearance less than 30 mL/min, see Cockcroft-Gault equation under **DOSE MODIFICATIONS**)
- suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see **PRECAUTIONS**)

CAUTION:

- severe hepatic dysfunction (total bilirubin greater than 50 micromol/L)

TESTS:

Baseline: CBC & diff, platelets, bilirubin, Alk phos, ALT, creatinine, and electroylytes
Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
Prior to each cycle: CBC & diff, platelets, creatinine, Bilirubin, Alk phos, ALT
For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.
Baseline and routine ECGs for patients at risk of developing QT prolongation (at the discretion of the ordering physician)
If clinically indicated at anytime: electrolytes, cardiac function

PREMEDICATIONS:

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

SUPPORTIVE MEASURES:

- all patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for management of diarrhea; proactive management of diarrhea is very important.
- topical emollients (eg, Bag Balm®, Udderly Smooth®) applied liberally and frequently to the hands and feet to reduce the symptoms hand-foot syndrome and lapatinib-induced rash, sunscreen for all sun exposed areas
- lapatinib-induced skin rash may respond to short-term oral steroids; topical or systemic antihistamines may be beneficial for pruritic reactions; antiseptic baths, potent local corticosteroids, and silver nitrate are recommended to treat paronychia; and topical or systemic antibiotics are indicated for superinfection

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
capecitabine*	1000 mg/m^2 BID x 14 days (d 1 to 14) (Total daily dose = 2000 to 2500 mg/m^2/day)	PO with food
lapatinib	1250 mg ONCE DAILY x 21 days (d 1 to 21)	PO at least one hour before or at least one hour after a low fat meal

* Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Repeat every 21 days x 6 to 8 cycles. Responding patient may be continued on treatment at the discretion of the treating physician. If discontinuing capecitabine for any reason other than progressive disease, and no severe toxicities to lapatinib, may continue lapatinib monotherapy till evidence of disease progression. Discontinue if no response after 2 cycles or unacceptable toxicity.
Note: combining lapatinib with any other chemotherapy drugs would require a separate CAP approval

Dose modifications of lapatinib and capecitabine may occur independently (i.e. the dose of lapatinib may be reduced while maintaining the starting dose of capecitabine, or vice versa)

- Maximum treatment delay of 2 weeks is allowed for resolution of toxicity. If delay of more than 2 weeks due to toxicity, the involved drug should be discontinued permanently.

1. Hematological – for capecitabine only

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
greater than or equal to 1.5	and	greater than or equal to 75	100%	100%	100%	100%
1 to 1.49	or	50 to 74.9	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
0.5 to 0.99	or	25 to 49.9	delay* then 75%	delay* then 50%	discontinue	discontinue
less than 0.5	or	less than 25	discontinue or delay* then 50%	discontinue	discontinue	discontinue

*delay until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L

2. Hand-Foot Skin Reaction

- if treatment is interrupted due to toxicity, retain the original stop and start dates (ie, do not make up for missed doses when treatment is resumed)

Grade	Hand-Foot Skin Reaction	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
1	Skin changes with discomfort (eg, numbness, dysesthesia, paresthesia, tingling, erythema) not disrupting normal activities	100%	100%	100%	100%
2	Skin changes with pain (eg, erythema, swelling) affecting activities of daily living	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	Severe skin changes with pain (eg, moist desquamation, ulceration, blistering) causing severe discomfort and inability to work or perform activities of daily living	delay* then 75%	discontinue or delay* then 50%	discontinue	discontinue

*stop treatment immediately and delay until resolved to grade 0 to 1

3. **Other Non-Hematological Toxicity**
   - see next table for toxicity grading criteria for **diarrhea, nausea and vomiting, and stomatitis**
   - if treatment is interrupted due to toxicity, retain the original stop and start dates (ie, do not make up for missed doses when treatment is resumed)

Toxicity Grade	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
0 to 1	100%	100%	100%	100%
2	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	delay* then 75%	delay* then 50%	discontinue	discontinue
4	discontinue or delay* then 50%	discontinue	discontinue	discontinue

*stop treatment immediately and delay until toxicity resolved to grade 0 to 1

Toxicity Criteria

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0 to 1	Increase of 2 to 3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4 to 6 stools/day or nocturnal stools	2 to 5 vomits/day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Increase of 7 to 9 stools/day or incontinence, malabsorption	6 to 10 vomits/day and cannot eat	Painful erythema, edema or ulcers and cannot eat
4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	10 vomits or more per day or requires parenteral support; dehydration	Mucosal necrosis, requires parenteral support

4. **Hepatic dysfunction**: Dose modification may be required. Capecitabine has not been studied in severe hepatic dysfunction. Lapatinib: moderate and severe impairment (ALT or AST greater than 3 times the upper limit of normal or total bilirubin greater than 2 times the upper limit of normal) have been associated with increased systemic exposure; consider dose reduction to 750 mg PO once daily; treatment should be stopped if severe hepatotoxicity develops.

5. **Renal dysfunction:** Capecitabine

Creatinine Clearance mL/min	Capecitabine Dose only
greater than 50	100%
30 to 50	75%
less than 30	Discontinue

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance (mL/min)} = \frac{\text{N (140 - age) wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.23 male
N = 1.04 female

6. **Pulmonary Toxicity**: Interstitial lung disease and pneumonitis have been associated with lapatinib treatment. Patients should be monitored for pulmonary symptoms, and treatment discontinued if reported symptoms are Grade 3 or greater.

7. **Cardiac Toxicity:** Lapatinib should be discontinued in patients with symptoms associated with decreased LVEF (grade 3 or greater), or if LVEF drops 20% or greater relative to baseline or below the lower limit of normal. Treatment may be reconsidered with a dose reduction from 1250 mg/day to 1000 mg/day after a minimum of 2 weeks, but only if LVEF recovers to normal and the patient is asymptomatic.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.

Capecitabine

2. **Dihydropyrimidine dehydrogenase (DPD) deficiency** can result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity - secondary to reduced drug metabolism of capecitabine. This deficiency is thought to be present in about 3% of the population.
3. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
4. **Possible drug interactions with capecitabine and warfarin, phenytoin or fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during capecitabine therapy and for 1 month after stopping capecitabine).

Lapatinib

5. Lapatinib is associated with **QT/QT_c prolongation**. Patients who are at risk for developing torsades de pointes (an atypical ventricular tachycardia with changes in QT interval) include

those with cardiac disease, history of arrhythmias, electrolyte disturbances, nutritional deficits, etc. and should be closely monitored. Baseline and periodic electrolyte measurements and electrocardiograms with QT measurement should be considered. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to lapatinib treatment. Concurrent therapy with other QT prolonging drugs may increase the risk of potentially fatal arrhythmias and should be avoided if possible

6. **Left ventricular ejection fraction (LVEF)** has been reported to decrease with lapatinib. Events are usually reversible and asymptomatic. Caution is advised in patients with conditions that impair left ventricular function. The majority of LVEF decreases (69%) occurred within the first 9 weeks of treatment during clinical trials, but long-term data is limited. Symptomatic events responded to standard CHF therapy in most. Baseline LVEF should be evaluated in all patients prior to initiation of treatment and periodically throughout treatment.
7. **Rash** generally mild to moderate in intensity. Skin rash generally appears on the trunk, and sometimes the face. Rash incidence does not appear to relate to dose, serum concentration or clinical response to treatment. Onset of rash and other dermatologic events tends to develop early in treatment, usually occurring in the first two months. Most dermatologic events with lapatinib monotherapy resolve without dose adjustment or treatment interruption. Treatment should be permanently discontinued for intolerable grade 3 or 4 reactions or for grade 3 or 4 reactions which recur after treatment interruption and rechallenge.
8. **Lapatinib** is extensively metabolized by CYP 3A4 and is also an inhibitor of CYP 3A4 and 2C8. Concurrent use with strong CYP 3A4 nhibitors or inducers should be avoided. Concurrent use with other QT/QT_c prolonging drugs (eg. amiodarone, sotalol, haloperidol, amitriptyline, methadone, fluconazole, erythromycin, ciprofloxacin, ondansetron, formoterol, quinidine, tacrolimus) should be avoided when possible. Current drug interaction database or BC Cancer Drug Manual should be consulted for more information.

Call Dr. Stephen Chia or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Cameron D, et al. Lapatinib plus capecitabine in women with HER-2 positive advanced breast cancer: final survival analysis of phase III randomized trial. Oncologist 2010;15:924-34.
2. Geyer CE, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-43.