BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using PERTuzumab, Trastuzumab, and DOCEtaxel as First-Line Treatment for Advanced Breast Cancer

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

ELIGIBILITY:

Patients must have:

- HER2-positive unresectable locally recurrent or metastatic breast cancer
  - HER-2 over-expression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 at a quality assured laboratory, and
- Previously untreated in the advanced setting, or
- Relapsed after at least 6 months of completing neoadjuvant or adjuvant trastuzumab-based protocol, or
- Relapsed on or after adjuvant trastuzumab emtansine (KADCYLA)

Patients should have:

- ECOG status 0 to 1
- Adequate renal and hepatic function
- Adequate hematological (ANC greater than 1.5 x 10^9/L and platelets greater than 100 x 10^9/L) function
- No signs or symptoms of cardiac disease. For patient with equivocal cardiac status, a MUGA scan or ECHO should be done and reveal a normal left ventricular ejection fraction.

EXCLUSIONS:

Patients must not have:

- 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 to 4
- Pregnancy or lactation
- Significant hepatic dysfunction
- Neoadjuvant therapy for locally advanced breast cancer is not funded

TESTS:

- Baseline: CBC & diff, platelets, total bilirubin, ALT. If clinically indicated: GGT, LDH, Alk Phos
- If clinically indicated: MUGA scan or echocardiogram at baseline and every 12 weeks during treatment is recommended but not mandatory
- Before each treatment for **Cycles 1 to 9** (cycles with docetaxel and the first cycle of PERTuzumab and trastuzumab only): CBC & diff, platelets
- For ongoing treatment with PERTuzumab and trastuzumab only: CBC & diff, platelets (optional and only if indicated)
- **Prior to Cycle 4**: total bilirubin, ALT, GGT, Alk Phos
- If clinically indicated at any time: total bilirubin, protein level, albumin, GGT, Alk Phos, LDH, ALT, urea, creatinine, echocardiogram or MUGA scan

PREMEDICATIONS:

- Not usually required for trastuzumab or PERTuzumab
- For DOCEtaxel:
  - dexamethasone 8 mg PO bid for 3 days, starting one day prior to each DOCEtaxel administration; patient must receive minimum of 3 doses pre-treatment
  - Additional antiemetics not usually required.
- DOCEtaxel-induced onycholysis and cutaneous toxicity of the hands may be prevented by wearing frozen gloves starting 15 minutes before DOCEtaxel infusion until 15 minutes after end of DOCEtaxel infusion; gloves should be changed after 45 minutes of wearing to ensure they remain cold during the entire DOCEtaxel infusion.

TREATMENT:

Cycle 1 – PERTuzumab (day 1) and trastuzumab (day 2) loading doses:

Drug	Dose	BC Cancer Administration Guideline
PERTuzumab	840 mg loading dose **Day 1**	IV in NS 250 mL over 1 hour Observe for 1 hour post-infusion
trastuzumab	8 mg/kg loading dose **Day 2**	IV in NS 250 mL over 1 hour 30 min Observe for 1 hour post-infusion.
DOCEtaxel	75 mg/m^2 **Day 2**	IV in NS 250 to 500 mL over 1 hour (use non-DEHP equipment)

Cycles 2 to 8 (all drugs may be given on the same day if cycle 1 tolerated):

Drug	Dose	BC Cancer Administration Guideline
PERTuzumab	420 mg	▪ IV in NS 250 mL over 1 hour on the second dose, observe for 30 minutes to 1 hour post infusion* ▪ IV in NS 250 ml over 30 minutes on all subsequent doses if no adverse reactions, observe for 30 minutes to 1 hour post infusion* **observation period not required after 3 consecutive treatments with no reaction*
trastuzumab	6 mg/kg	▪ IV in NS 250 mL over 1 hour on the second dose, observe for 30 minutes post infusion*, ▪ IV in NS 250 ml over 30 minutes on all subsequent doses if no adverse reactions, observe for 30 min post infusion* **observation period not required after 3 consecutive treatments with no reaction*
DOCEtaxel (6 to 8 cycles only)	75 mg/m^2 †	IV in NS 250 to 500 mL over 1 hour (use non-DEHP equipment)

† may consider dose escalation to 100 mg/m^2 if patient tolerates a least one cycle of 75 mg/m^2 **without** any of the following events: febrile neutropenia, grade 4 neutropenia for greater than 5 days, any ANC less than 0.1 x 10^9/L for greater than 1 day, or other non-hematological toxicities greater or equal to 3.

Maintenance PERTuzumab and trastuzumab:

Drug	Dose	BC Cancer Administration Guideline
PERTuzumab	420 mg	IV in NS 250 ml over 30 minutes on all subsequent doses if no adverse reactions
trastuzumab	6 mg/kg	IV in NS 250 ml over 30 minutes on all subsequent doses if no adverse reactions

Repeat every 21 days in responding patients. Give DOCEtaxel for up to 6 to 8 cycles unless disease progression or unacceptable toxicity. PERTuzumab and trastuzumab should be continued every 21 or 28 days after discontinuation of DOCEtaxel in responding patients without disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

1. PERTuzumab and Trastuzumab:

- Dose reductions are not recommended. Doses are held or discontinued due to toxicity.
- Discontinue PERTuzumab if trastuzumab is discontinued.
- Patient may continue to receive both PERTuzumab and trastuzumab if docetaxel is discontinued due to toxicity or after 6-8 cycles and without evidence of disease progression.

Missed Doses

- Re-load PERTuzumab if the time between 2 sequential infusions is greater than 6 weeks.
- Re-load trastuzumab if the time between 2 sequential infusions is greater than 6 weeks.
- If re-loading is required for either drug, the 3 drugs should be given in the same schedule as Cycle 1 (e.g. PERTuzumab day 1, trastuzumab and docetaxel day 2).
- The next cycle should follow 21 days from the re-loading dose.
  - Continue treatment with 21-day dosing cycle
  - After 6 to 8 consecutive cycles, may switch to 28-day dosing cycles

Cardiotoxicity[4] – PERTuzumab and Trastuzumab

Left Ventricular Ejection Fraction	**PERTuzumab and Trastuzumab**		
	Action	**LVEF at Re-assessment†**	**Subsequent Action**
a drop in LVEF to less than 40% and asymptomatic	Hold and repeat MUGA or echocardiogram in 3 weeks	▪ recovered to greater than 45% OR ▪ 40-45% and less than 10%-points from baseline	Restart
40-50% AND greater than 10%-points below baseline value and asymptomatic		▪ less than 40% OR ▪ 40-50% AND greater than 10%-points below baseline value and asymptomatic ▪ symptomatic	Discontinue
Symptomatic	Consider discontinuing	n/a	n/a

† If after repeat assessment within approximately 3 weeks, the LVEF has not improved, or declined further, discontinuation of PERTuzumab and trastuzumab should be strongly considered.

2. DOCEtaxel:

2a. Hematological

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose	filgrastim (G-CSF)option
greater than or equal to 1.5	and	greater than or equal to 100	100%	
1.0 to less than 1.5		70 to less than 100	75%†	give 100% dose with G-CSF 300 mcg sc daily on days 4 to 11 (adjust as needed)
less than 1.0	or	less than 70	delay until ANC greater than or equal to 1.5 and platelets greater than 100 than give 75% dose	delay until ANC greater than or equal to 1.5 and platelets greater than 100 than give 100% dose with G-CSF 300 mcg sc daily on days 4 to 11 (adjust as needed)
Febrile neutropenia or grade 4 neutropenia lasting greater than or equal to 7 days in previous cycle			give 75% dose or filgrastim option	

† Dose may be re-escalated to 100% at next cycle if ANC greater than or equal to 1.5 and platelets greater than 100 at the discretion of the treating physician.

2b. Hepatic Dysfunction

Alkaline Phosphatase		ALT		Bilirubin	Dose
less than 2.5 x ULN	and	less than or equal to 1.5 x ULN	--	--	100%
2.5 to 6 x ULN	and	1.6 to 3.5 x ULN	--	--	75%
greater than 6 x ULN	or	greater than 3.5 ULN	or	greater than ULN	discuss with contact physician

ULN = upper limit of normal

PRECAUTIONS:

1. **Cardiac toxicity:** Decreases in LVEF have been reported with drugs that block HER2 acitivity, including PERTuzumab. However, PERTuzumab does not seem to further increase the incidence of symptomatic congestive heart failure or decreased LVEF when used in combination with trastuzumab and docetaxel. Trastuzumab can produce declines in ventricular dysfunction and congestive heart failure (CHF). Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias/events. Most patients who develop congestive heart failure respond to appropriate medical therapy and in some cases (where the benefit outweighs the risk) may continue treatment under close medical supervision.
2. **PERTuzumab or Trastuzumab infusion-associated symptoms,** usually chills and fever, occur in 40% of patients during the first trastuzumab infusion (infrequent with subsequent infusions). Other signs and symptoms may include nausea, vomiting, pain (sometimes at tumour sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. Symptoms may be treated with acetaminophen, diphenhydrAMINE and meperidine with or without an infusion rate reduction. Rarely, serious infusion-related reactions have been reported (3 per 1000 patients) sometimes leading to death (4 per 10,000). Reactions include dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, and, uncommonly, allergic-like reactions. Patients experiencing dyspnea at rest due to pulmonary metastases and other pulmonary/cardiac conditions may be at increased risk of a fatal infusion reaction and should be treated with extreme caution, if at all. For serious reactions, discontinue the infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.
3. **DOCEtaxel Hypersensitivity:** Reactions are common but it is not necessary to routinely initiate the infusion slowly. If slow initiation of infusion is needed, start infusion at 30 mL/h x 5 minutes, then 60 mL/h x 5 minutes, then 120 mL/h x 5 minutes, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 minutes and then complete infusion at 500 mL/h). Refer to BC Cancer Hypersensitivity Guidelines
4. **Fluid retention:** Dexamethasone premedication must be given to reduce incidence and severity of fluid retention.
5. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
6. **Extravasation:** DOCEtaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
7. **Hepatic Dysfunction:** DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST or ALT) may lead to increased toxicity and usually requires a dose reduction. Baseline liver enzymes are recommended before cycle 1 and then if clinically indicated (eg, repeat liver enzymes prior to each treatment if liver enzymes are elevated, liver metastases are present or there is severe toxicity such as neutropenia). If liver enzymes are normal and there is no evidence of liver metastases or severe toxicity, check liver enzymes after 3 cycles (ie, at cycle 4). Note: this information is intended to provide guidance but physicians must use their clinical judgment when making decisions regarding monitoring and dose adjustments

8. **A possible interaction between trastuzumab and warfarin** has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then weekly for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed. (JAMA 1999;282:2299-301)

Call Dr. Stephen Chia or tumour group delegate at 604-877-600 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366(2):10919.
2. Swain SM, Ewer MS, Cortés J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist 2013;18(3):25764**.**
3. Swain SM, Kim SB, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013;14(6):46171.
4. Hoffmann-La Roche Limited. PERJETA® product monograph. Mississauga, Ontario; 12 April 2013.
5. Keating, GM. Pertuzumab in the First-Line Treatment of HER2-Positive Metastatic Breast Cancer. Drugs 2012; 72 (3): 353-360.