

BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer Using PERTuzumab, Trastuzumab (HERCEPTIN), and PACLitaxel as First-Line Treatment for Advanced Breast Cancer

Protocol Code: BRAVPTRAT
Tumour Group: Breast
Contact Physician: Dr. Sophie Sun

ELIGIBILITY:

- First-line treatment of patients with HER2-positive unresectable locally recurrent or metastatic breast cancer (patients may have received trastuzumab in the neoadjuvant or adjuvant setting, but must be relapse free for 6 months or greater)
- Over-expression of HER-2
- HER-2 over-expression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 or HER2 copy number greater than or equal to 6.0 at a quality assured laboratory
- Life expectancy greater than 3 months
- ECOG status 0-1
- Adequate renal and hepatic function
- Adequate hematological (ANC greater than $1.5 \times 10^9/L$ and platelets greater than $100 \times 10^9/L$) 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:

- 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
- 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, CA 15-3
- 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 PACLitaxel 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, albumin, ALT, GGT, alk phos, LDH, BUN, creatinine, echocardiogram or MUGA scan

PREMEDICATIONS:

- Not usually required for trastuzumab or PERTuzumab
- For PACLitaxel: **PACLitaxel must not be started unless the following drugs have been given:**
 - 45 minutes prior to PACLitaxel give dexamethasone 20 mg IV in NS 50 mL over 15 minutes
 - 30 minutes prior to PACLitaxel give diphenhydramine 50 mg IV and ranitidine 50 mg IV in 50 mL over 20 minutes (compatible up to 3 hours when mixed in bag)
 - additional anti-emetics are not usually required
- If hypersensitivity reactions occur, premedications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV premedications given 30 minutes prior to PACLitaxel: dexamethasone 10 mg, diphenhydramine 25 mg, and H₂-antagonist (e.g., ranitidine 50 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- Additional antiemetics not usually required.

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 (HERCEPTIN)	8 mg/kg loading dose Day 2	IV in NS 250 mL over 1 hour 30 min Observe for 1 hour post-infusion.
PACLitaxel*	175 mg/m ² Day 2	IV in 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller in-line filter)

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	<ul style="list-style-type: none"> 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** <p><i>**observation period not required after 3 consecutive treatments with no reaction</i></p>
trastuzumab (HERCEPTIN)	6 mg/kg	<ul style="list-style-type: none"> 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** <p><i>**observation period not required after 3 consecutive treatments with no reaction</i></p>
PACLitaxel (6 to 8 cycles only)	175 mg/m ²	IV in 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller in-line filter)

Maintenance PERTuzumab and trastuzumab (HERCEPTIN®):

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 (HERCEPTIN)	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 PACLitaxel for up to 6 to 8 cycles unless disease progression or unacceptable toxicity. PERTuzumab and trastuzumab should be continued every 21 days after discontinuation of PACLitaxel 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 PACLitaxel 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 [PACLitaxel](#) day 2).
- The next cycle should follow 3 weeks from the re-loading dose.

Cardiotoxicity⁴ – PERTuzumab and Trastuzumab (HERCEPTIN[®])

Left Ventricular Ejection Fraction	PERTuzumab and Trastuzumab (HERCEPTIN [®])		
	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	<ul style="list-style-type: none">▪ 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		<ul style="list-style-type: none">▪ 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. PACLitaxel:

2a. Hematological

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	Dose
Greater than or equal to 1.5	and	Greater than or equal to 90	175 mg/m ²
1.0 to less than 1.5	or	70 to less than 90	150 mg/m ²
Less than 1.0	or	Less than 70	delay

2b. Hepatic Dysfunction

AST +/- ALT		Bilirubin	Dose
Less than 10 x ULN	and	Less than or equal to 1.25 x ULN	175 mg/m ²
Less than 10 x ULN	and	1.26-2 x ULN	135 mg/m ²
Less than 10 x ULN	and	2.01-5 x ULN	90 mg/m ²
Greater than or equal to 10 x ULN	or	Less than 5 x ULN	Not recommended

ULN = upper limit of normal

2c. Arthralgia and/or myalgia: If arthralgia and/or myalgia from PACLitaxel of grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (TYLENOL #3®) a limited number of studies report a possible therapeutic benefit from the following:

- prednisone 10 mg PO BID x 5 days starting 24 hours post PACLitaxel
- gabapentin 300 mg PO on day prior to PACLitaxel, 300 mg PO BID on treatment day and then 300 mg PO TID x 7 to 10 days

2d. Neuropathy: Dose modification or discontinuation for PACLitaxel may be required. Refer to BC Cancer Drug Manual.

PRECAUTIONS:

- 1. Cardiac toxicity:** Decreases in LVEF have been reported with drugs that block HER2 activity, 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 PACLitaxel. 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. **Fluid retention:** Dexamethasone premedication must be given to reduce incidence and severity of fluid retention.
4. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated. Refer to [BC Cancer Extravasation Guidelines](#).
6. **Hepatic Dysfunction:** PACLitaxel undergoes hepatic metabolism. Dose adjustments may be required.
7. **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).
8. **PACLitaxel Hypersensitivity:** Reactions are common with PACLitaxel. Refer to [BC Cancer Hypersensitivity Guidelines](#).

<u>Mild</u> symptoms (e.g. mild flushing, rash, pruritus)	<ul style="list-style-type: none"> ▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
<u>moderate</u> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	<ul style="list-style-type: none"> ▪ stop PACLitaxel infusion ▪ give IV diphenhydramine 25 to 50 mg and hydrocortisone IV 100 mg ▪ after recovery of symptoms resume PACLitaxel infusion at 20 mL/h for 5 minutes, 30 mL/h for 5 minutes, 40 mL/h for 5 minutes, then 60 mL/h for 5 minutes. If no reaction, increase to full rate. ▪ if reaction recurs, discontinue PACLitaxel therapy
<u>severe</u> symptoms (i.e. <u>one</u> or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	<ul style="list-style-type: none"> ▪ stop PACLitaxel infusion ▪ give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

9. Extravasation: PACLitaxel causes pain and tissue necrosis if extravasated. Refer to [BC Cancer](#) Extravasation Guidelines.

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

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

References:

1. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer. *J Clin Oncol* 2015;33:442-47.
2. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015;372:724-34.
3. Yu AF, Manrique C, Pun S, et al. Cardiac safety of paclitaxel plus trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer. *The Oncologist* 2016;21(4):418–24.