

# **BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN®), PACLitaxel and CARBOplatin as First-Line Treatment for Advanced Breast Cancer**

**Protocol Code:**

*BRAVTPC*

**Tumour Group:**

*Breast*

**Contact Physician:**

*Dr. Karen Gelmon*

## **ELIGIBILITY:**

- Overexpression of HER-2 neu
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BCCA central laboratory
- Patient ineligible for, or unwilling to participate in, a clinical trial
- Life expectancy greater than 3 months
- ECOG status 0-2
- 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.
- A “Class II Drug Registration Form” must be submitted for Trastuzumab at the time of initiation of treatment.

## **EXCLUSIONS:**

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Pre-existing motor or neuropathy greater than grade 2 (symptomatic, interfering with activities of daily living, or disabling)

## **TESTS:**

- Baseline: CBC & diff, platelets, total bilirubin, AST, creatinine, camera nuclear renogram for GFR (if available)
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Before each treatment: CBC & diff, platelets, creatinine
- If clinically indicated before each treatment: total bilirubin, AST
- If clinically indicated at any time: cardiac function

**PREMEDICATIONS:**

- Not usually required for trastuzumab
- **PACLitaxel must not be started unless the following drugs have been given:**  
45 minutes prior to PACLitaxel:
  - Dexamethasone 20 mg IV in 50 mL NS over 15 minutes
 30 minutes prior to PACLitaxel:
  - DiphenhydrAMINE 50 mg IV and Ranitidine 50 mg IV in 50 mL NS over 20 minutes (compatible up to 3 hours when mixed in bag)
- Ondansetron 8 mg po 30 minutes pre-CARBOplatin

**TREATMENT:**

Cycle	1				2			3			
Week	1	1	2	3	4	5	6	7	8	9	
Day	1	2	8	15	1	8	15	1	8	15	etc
Trastuzumab	X				X			X			
PACLitaxel		X			X			X			
CARBOplatin		X			X			X			

PACLitaxel and CARBOplatin are given on day 2 for cycle 1 only. In subsequent cycles, PACLitaxel and CARBOplatin are given after trastuzumab on day 1.

Repeat every 21 days x 6 cycles. Discontinue if no response after 2 cycles.

Note: To continue single agent trastuzumab after completion of cycle 6, see protocol BRAVTR.

**Cycle 1****Day 1**

Drug	Dose	BCCA Administration Guideline
Trastuzumab (HERCEPTIN®)	8 mg/kg Day 1 only	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion**

**Day 2**

Drug	Dose	BCCA Administration Guideline
PACLitaxel (TAXOL®)	175 mg/m <sup>2</sup> Day 2 only	IV in 250 to 500 mL NS over 3 hours (use non-PVC equipment, in-line filter)
CARBOplatin	AUC* x (GFR + 25)	IV in 250 mL D5W over 30 minutes

\* use AUC of 6; if extensive prior radiation therapy, use AUC of 5

Measured GFR (e.g. nuclear renogram) is preferred whenever feasible, *particularly* in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, etc.). The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR; the estimated GFR reported by the lab or calculated using the Cockcroft-Gault equation should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

#### Cockcroft-Gault Formula

$$\text{GFR} = \frac{1.04 \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

Note: The same method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

#### Cycles 2 - 6

Drug	Dose	BCCA Administration Guideline
Trastuzumab (HERCEPTIN®)	6 mg/kg	<ul style="list-style-type: none"> <li>IV in 250 mL NS over 1 hour on the second dose, observe for 30 minutes post infusion**,</li> <li>IV IN 250 ml NS over 30 min on all subsequent doses if no adverse reactions, observe for 30 min post infusion**</li> </ul> then start PACLitaxel premedications
PACLitaxel (TAXOL®)	175 mg/m <sup>2</sup>	IV in 500 mL NS over 3 hours (use non-PVC equipment, in-line filter)
CARBOplatin	AUC* x (GFR + 25)	IV in 250 mL D5W over 30 minutes

\* use AUC of 6; if extensive prior radiation therapy, use AUC of 5

\*\*observation period not required after 3 consecutive treatments with no reaction

Repeat every 21 days x 6 cycles. Discontinue if no response after 2 cycles.

## DOSE MODIFICATIONS:

### 1. Trastuzumab:

None required. Discontinue if unacceptable toxicity occurs.

### 2. Hematological Modifications

ANC (x 10 <sup>9</sup> /L)	Platelets (x 10 <sup>9</sup> /L)	Dose (both drugs)
greater than or equal to 1.5	greater than or equal to 90	100%
1 -1.49	70-89	75%
less than 1	less than 70	Delay*

\*If repeated delays or dose reductions, consider reducing CARBOplatin to AUC of 5 from 6, or 4 from 5

### 3. Hepatic Dysfunction (PACLitaxel only)

Bilirubin (micromol/L)		AST	Dose
less than or equal to 25	and	less than 2 x ULN	175 mg/m <sup>2</sup>
less than or equal to 25	and	greater than or equal to 2 x ULN with no liver metastases or greater than or equal to 5 x ULN with liver metastases	135 mg/m <sup>2</sup>
25-50			75 mg/m <sup>2</sup>
greater than 50			50 mg/m <sup>2</sup>

ULN = upper limit of normal

4. **Neuropathy:** Dose modification or discontinuation of PACLitaxel may be required (see BCCA Cancer Drug Manual).

5. **Arthralgia and/or myalgia:** If arthralgia and/or myalgia of grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (e.g., TYLENOL #3®), a limited number of studies report a possible therapeutic benefit using:

- Prednisone 10 mg po bid x 5 days starting 24 hours post-PACLitaxel
- Gabapentin 300 mg po on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 7-10 days

If arthralgia and/or myalgia persist, reduce subsequent PACLitaxel doses to 135 mg/m<sup>2</sup>.

6. **Renal dysfunction:** If significant increase (greater than 20%) in creatinine, repeat nuclear renogram (if available) and recalculate CARBOplatin dose using new GFR.
7. **Gastrointestinal toxicity:** If greater than or equal to grade 3 mucositis occurs, PACLitaxel and CARBOplatin should be withheld until resolution to less than or equal to grade 1, then reinstated at 80% of previous dose

## PRECAUTIONS:

1. **Cardiac toxicity:** Trastuzumab can produce ventricular dysfunction and congestive heart failure in about 2-4% of patients. The majority of patients who develop cardiac dysfunction are symptomatic. Regular monitoring of asymptomatic patients is not routinely necessary but may be ordered within 4-6 months of treatment with trastuzumab. If no significant decline in cardiac function is apparent, repeated testing is not generally necessary, unless the patient's medical condition changes. Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias. Most patients who develop cardiac dysfunction respond to appropriate medical therapy and in some cases (where the benefit outweighs the risk) may continue trastuzumab under close medical supervision.
2. **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 trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.
3. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.

4. **Hypersensitivity:** Reactions are common with PACLitaxel. See BCCA Hypersensitivity Guidelines.

<u>Mild</u> symptoms (e.g. mild flushing, rash, pruritus)	<ul style="list-style-type: none"> <li>▪ complete PACLitaxel infusion. Supervise at bedside</li> <li>▪ no treatment required</li> </ul>
<u>moderate</u> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	<ul style="list-style-type: none"> <li>▪ stop PACLitaxel infusion</li> <li>▪ give IV DiphenhydrAMINE 25-50 mg and Hydrocortisone IV 100 mg</li> <li>▪ 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.</li> <li>▪ if reaction recurs, discontinue PACLitaxel therapy</li> </ul>
<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"> <li>▪ stop PACLitaxel infusion</li> <li>▪ give IV antihistamine and steroid as above. Add Epinephrine or bronchodilators if indicated</li> <li>▪ discontinue PACLitaxel therapy</li> </ul>

5. **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.

6. **A possible interaction with warfarin and trastuzumab** 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. Karen Gelmon or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

Date activated: 01 October 2004

Date revised: 01 June 2011 (Infusion section revised)

**References:**

1. Robert N, Leyland-Jones B, Asmar L et al. Phase III comparative study of trastuzumab and PACLitaxel with and without CARBOplatin in patients with HER-2/neu positive advanced breast cancer. Breast Cancer Res Treat 2002;76(suppl 1):S35.
2. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. J Clin Oncol 2004;22:322-329