

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

Protocol Code:

BRAVTRAP

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.

EXCLUSIONS:

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)

TESTS:

- Baseline: CBC & diff, platelets, total bilirubin, AST
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Before each PACLitaxel treatment: CBC & diff, platelets
- If clinically indicated before each PACLitaxel 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 NS 50 mL over 15 minutes
 - 30 minutes prior to PACLitaxel:
 - diphenhydramine 50 mg IV and Ranitidine 50 mg IV in NS 50 mL over 20 minutes (compatible up to 3 hours when mixed in bag)
- Additional antiemetics not usually required.

TREATMENT:

Cycle	1				2			3			etc
Week	1	1	2	3	4	5	6	7	8	9	
Day	1	2	8	15	1	8	15	1	8	15	
trastuzumab (HERCEPTIN)	X				X			X			
PACLitaxel		X			X			X			

PACLitaxel is given on day 2 for cycle 1 only. In subsequent cycles, PACLitaxel is 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 2 NS 50 mL over 1 hour 30 min Observe for 1 hour post-infusion**

Day 2

Drug	Dose	BCCA Administration Guideline
PACLitaxel	175 mg/m ² Day 2 only	IV in NS 500 mL* over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller in-line filter)

*use 250 mL for doses less than 150 mg

Cycles 2 - 6
Day 1

Drug	Dose	BCCA Administration Guideline
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 min on all subsequent doses if no adverse reactions, observe for 30 min post infusion**
PACLitaxel	175 mg/m ²	IV in NS 500 mL* over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller in-line filter)

*use 250 mL for doses less than 150 mg

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

DOSE MODIFICATIONS:

1. Trastuzumab:

None required. Discontinue if unacceptable toxicity occurs.

2. PACLitaxel:

2a. Hematological

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose	Dose after neutropenic sepsis on PACLitaxel
greater than or equal to 1.5	and	greater than 90	175 mg/m ²	135 mg/m ²
1 to 1.4	or	70 to 90	135 mg/m ²	135 mg/m ²
less than 1	or	less than 70	delay	delay

2b. Hepatic Dysfunction

Bilirubin (micromol/L)		AST	Dose
less than or equal to 25	and	less than 2 x ULN	175 mg/m ²
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 ²
25 to 50			75 mg/m ²
greater than 50			50 mg/m ²

ULN = upper limit of normal

2c. Neuropathy: Dose modification or discontinuation may be required (see BCCA Cancer Drug Manual).

2d. 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 to 10 days

If arthralgia and/or myalgia persist, reduce subsequent PACLitaxel doses to 135 mg/m².

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 to 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"> ▪ 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 25-50 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

5. **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
6. **A possible interaction with 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. 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 Nov 1999

Date revised: 1 Aug 2016 (Class II registration deleted, size of filter specified, TALLman lettering formatted)

References:

1. Slamon D, Leyland-Jones B, Shak S, Paton V et al. Addition of Herceptin™ (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2 +/MBC) markedly increases anticancer activity: a randomized, multinational controlled phase III trial. Proc Am Soc Clin Oncol 1998;17:98a.
2. Gelmon K, Arnold A, Verma S et al. Pharmacokinetics (PK) and safety of trastuzumab (Herceptin®) when administered every three weeks to women with metastatic breast cancer. [Abstract 271] Proc Am Soc Clin Oncol 2001;20(1):69a.
3. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. J Clin Oncol 2004;22:322-329.