# BC Cancer Protocol Summary for Adjuvant Therapy for Breast Cancer using Weekly PACLitaxel and Trastuzumab

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| ***Protocol Code:*** | ***BRAJTTW*** |
| ***Tumour Group:*** | ***Breast*** |
| ***Contact Physician:*** | ***Dr.*** *Nathalie LeVasseur* |

**ELIGIBILITY**:
- Overexpression of HER-2 neu
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- Tumor size less than or equal to 3 cm
- Node negative
- ECOG status 0-2
- Adequate hematopoietic and hepatic function
- No clinically significant cardiac disease
- LVEF greater than or equal to 50%*
  * If the LVEF is between 45-50%, may treat at physician's discretion

**EXCLUSIONS**:
- Significant cardiovascular disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months) and/or LVEF less than 50%; if initial reading is less than 50%, physician may consider repeating for validity, or assessing LVEF by the other modality, e.g. echocardiogram instead of MUGA

**TESTS**:
- Baseline: CBC & diff, platelets, total bilirubin, ALT
- Baseline if clinically indicated: cardiac function (echocardiogram or MUGA scan)
- Before each treatment: CBC & diff, platelets
- If clinically indicated: total bilirubin, ALT or 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 10 mg IV in NS 50 mL over 15 minutes
  - 30 minutes prior to PACLitaxel: diphenhydrAMINE 25 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)
- **NOTE:** If no PACLitaxel infusion reactions occur, no premedications may be needed for subsequent Day 8 and 15 PACLitaxel doses and may be omitted at physician's discretion.

- If infusion 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 20 mg, diphenhydrAMINE 50 mg, and $H_2$-antagonist (e.g., famotidine 20 mg). If no infusion reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.

- Additional antiemetics not usually required.

**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 | X | X | X | X | X | X | |

**PACLitaxel is given on day 2 for cycle 1 only. In subsequent cycles, PACLitaxel is given after trastuzumab on day 1.**

**1 cycle = 3 weeks,** Repeat every 21 days x 4 cycles.

- Followed by 13 consecutive cycles of trastuzumab to start 21 days after the final cycle of PACLitaxel/trastuzumab for a total of 1 year of trastuzumab treatment (maximum of 17 cycles of trastuzumab. See BC Cancer Protocol **BRAJTR**.

## Cycle 1, Week 1

### Day 1

| **Drug** | **Dose** | **BC Cancer Administration Guideline** |
|---|---|---|
| trastuzumab | 8 mg/kg<br>Day 1 only | IV in NS 250 mL over 1 hour 30 min<br>Observe for 1 hour post-infusion |

**Day 2**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| PACLitaxel | 80 mg/m$^2$<br>Day 2 only | IV in 100 to 500 mL (non-DEHP bag) NS over 1 hour<br>(use non-DEHP tubing with 0.2 micron in-line filter) |

**Cycle 1, Weeks 2 - 3**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| PACLitaxel | 80 mg/m$^2$ | IV in 100 to 500 mL (non-DEHP bag) NS over 1 hour<br>(use non-DEHP tubing with 0.2 micron in-line filter) |

**Cycles 2-4**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| trastuzumab | 6 mg/kg | IV in 250 ml NS over 1 hour on the second dose, observe for 30 minutes post infusion<br>IV IN 250 ml NS over 30 min on all subsequent doses if no adverse reactions, observe for 30 min post infusion**<br>then start PACLitaxel premedications |
| PACLitaxel | 80 mg/m$^2$ | IV in 100 to 250 mL (non-DEHP bag) NS over 1 hour once weekly x 3 weeks<br>(use non-DEHP tubing with 0.2 micron in-line filter) |

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

**DOSE MODIFICATIONS**:

1. **Trastuzumab**:

**1a. Cardiac Dysfunction**

**Asymptomatic Patients – Trastuzumab continuation based on serial LVEFs**

| Relationship of LVEF to LLN | Absolute Decrease Of less than 10 points from baseline | Absolute Decrease Of 10 -15 points from baseline | Absolute Decrease Of greater than or equal to 16 points from baseline |
|---|---|---|---|
| Within Normal Limits | Continue | Continue | Hold * |
| 1-5 points below LLN | Continue | Hold * | Hold * |
| greater than or equal to 6 points below LLN | Continue * | Hold * | Hold * |

- *Repeat LVEF assessment after 3-4 weeks, consider cardiac assessment
- If criteria for continuation are met – resume trastuzumab
- If 2 consecutive holds or a total of 3 holds occur, discontinue trastuzumab

**Symptomatic Patients**

- Symptomatic patients with evidence of cardiac dysfunction should have trastuzumab discontinued

For evidence of cardiac dysfunction likely related to trastuzumab and/or chemotherapy protocols, consider consulting a cardiologist, or review the following reference:
Curr Oncol 2008;15(1):24-31.

**1b. Weight**

Weight will be measured at each scheduled physician's visit. Dose changes based on weight will be made at this time unless the patient reports a significant weight change between physician visits.

**1c. Treatment Interruptions**
If an interruption in treatment of greater than 6 weeks occurs (ie more than 6 weeks has elapsed since the last treatment was given), occurs, consider repeating the loading dose of 8 mg/kg, and then resume usual dosing.

2. **PACLitaxel**:

2a. **Hematological toxicity**

| ANC (x $10^9$/L) | | Platelets (x $10^9$/L) | Dose | Dose after Neutropenic Sepsis |
|---|---|---|---|---|
| Greater than or equal to 1.0 | and | Greater than or equal to 90 | 80 mg/m$^2$ | 65 mg/m$^2$ |
| Less than 1.0 | or | Less than 90 | Contact Physician: Delay treatment. Physician may choose to reduce next dose to 65mg/m$^2$ or add filgrastim | delay |

**2b. Non-hematologic toxicity**

| Grade | Dose |
|---|---|
| Grade 2 motor or sensory neuropathy | Decrease dose of paclitaxel by 10 mg/m$^2$ |
| All other grade 2 non-hematological toxicity | Hold treatment until toxicity resolved to less than or equal grade 1<br>Decrease subsequent doses by 10 mg/m$^2$ |
| Greater than or equal to Grade 3 | Discontinue treatment |

2c. **Hepatic Dysfunction**

| ALT or AST | | Total bilirubin | Dose (mg/m$^2$) |
|---|---|---|---|
| less than 10 x ULN | and | less than or equal to 1.25 x ULN | 80 |
| less than 10 x ULN | and | 1.26 to 2 x ULN | 60 |
| less than 10 x ULN | and | 2.01 to 5 x ULN | 40 |
| greater than or equal to 10 x ULN | and/or | greater than 5 x ULN | not recommended |

ULN = upper limit of normal

2d. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Cancer Drug Manual).

2e. **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 65 mg/m$^2$.

## 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. **Infusion-related reactions**: Reactions are common with PACLitaxel. See BC Cancer SCDRUGRX.

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| *Mild* symptoms (e.g. mild flushing, rash, pruritus) | ▪ complete PACLitaxel infusion. Supervise at bedside<br>▪ no treatment required |
| *moderate* symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension | ▪ stop PACLitaxel infusion<br>▪ give IV diphenhydrAMINE 50 mg and Hydrocortisone IV 100 mg<br>▪ 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.<br>▪ if reaction recurs, discontinue PACLitaxel therapy |
| *severe* symptoms (i.e. *one* or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy) | ▪ stop PACLitaxel infusion<br>▪ give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated<br>▪ discontinue PACLitaxel therapy |

Alternative therapy with protocol BRAJPNT is available for moderate to severe hypersensitivity reaction that occurs despite premedications, or in those patients who cannot be managed with premedications due to a strong contraindication.

5. **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer 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. Nathalie LeVasseur or tumour group delegate at (604) 930-2098 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

## References:


1. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372:134-41.
2. 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.
3. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. J Clin Oncol 2004;22:322-329.
4. Nissenblatt MJ, Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment. JAMA. 1999;282(24):2299-301.
5. Mackey JR, Clemons M, Cote MA, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol 2008;15(1):24-31.