BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Breast Cancer using DOXOrubicin and Cyclophosphamide followed by PACLitaxel and Trastuzumab

Protocol Code	*BRAJACTT*
Tumour Group	*Breast*
Contact Physician	*Dr. Nathalie LeVasseur*

ELIGIBILITY:

Patient must have:

- 1 or more axillary lymph node metastasis(es), ***or*** node negative but with high risk of recurrence (see Cancer Management Guidelines for categories of risk), including patient with T1b disease (T1a still requires CAP approval)
- HER-2 over-expression defined as either IHC 3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- Anticipated survival of greater than 5 years

Patient should have:

- ECOG 0-2
- Adequate marrow, renal, and hepatic function
- No clinically significant cardiac disease
- LVEF greater than or equal to 50%*
  * If the LVEF is between 45-50%, the oncologist may decide to treat based on clinical assessment

Note:

- Primary prophylaxis with G-CSF is not mandatory, but may be considered if patient has one or more of the following risk factors:
  - Prior chemotherapy or radiation therapy
  - Persistent neutropenia
  - Recent surgery and/or open wounds
  - Liver dysfunction
  - Renal dysfunction
  - Older than 65 years of age and receiving full chemotherapy dose intensity

EXCLUSIONS:

- Pregnancy
- Significant cardiovascular disease 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, total bilirubin, ALT (ALT and total bilirubin should be measured prior to first cycle of AC and first cycle of PACLitaxel)
- Baseline, if clinically indicated: creatinine, GGT, LDH, alkaline phosphatase, MUGA scan or echocardiogram

- Before each treatment: CBC & Diff
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab and every 3-4 months until completion of treatment per the discretion of the treating physician. The maximum time between cardiac monitoring should be 4 months (see dose modification #6 for adjustment of trastuzumab based on changes in LVEF)
- If clinically indicated: creatinine; MUGA scan or echocardiogram, total bilirubin, ALT

PREMEDICATIONS:

- For the 4 cycles of DOXOrubicin and cyclophosphamide: Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

- For the 4 cycles of PACLitaxel: **PACLitaxel must not be started unless the following drugs have been given:**
  - 45 minutes prior to PACLitaxel give dexamethasone 20 mg IV in 50 mL NS over 15 minutes
  - 30 minutes prior to PACLitaxel give diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)
  - 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 20 mg, diphenhydramine 50 mg, and H_2-antagonist (e.g., famotidine 20 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- For trastuzumab: not usually required

TREATMENT:

Cycles 1 to 4

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	60 mg/m²	IV push
cyclophosphamide	600 mg/m²	IV in 100 to 250 mL NS over 20 min to 1 hour

Repeat every 21 days x 4 cycles.

- 4 consecutive cycles of PACLitaxel concurrent with trastuzumab to start **21 days after** final cycle of DOXOrubicin and cyclophosphamide

Cycle 5 – DAY 1

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

Cycle 5 – DAY 2

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel	175 mg/m^2 Day 2 only	IV in 250 to 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)

Cycle 6, 7, and 8

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*, • IV IN 250 ml NS over 30 min on all subsequent doses if no adverse reactions, observe for 30 min post infusion* then start PACLitaxel premedications
PACLitaxel	175 mg/m^2	IV in 250 to 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)

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

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**.

Radiation:
For patients with indications for radiation, the radiation treatment should be given at the usual time after the completion of the chemotherapy with the trastuzumab continued during the radiation therapy. There has been no increased toxicity reported in the clinical trials at this time, but there is no long term data; therefore, patients should be monitored. There have been no studies of concurrent trastuzumab and internal mammary node radiation, so it is unclear at this time whether there would be an enhanced risk of cardiotoxicity. If there is an anticipated need for internal mammary node radiation, it may be helpful to discuss the overall treatment program and timing with the treating radiation oncologist at the outset of chemotherapy.

DOSE MODIFICATIONS:

1. **Hematological (for Day 1 counts)**

For cycles of DOXOrubicin and cyclophosphamide only:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (both drugs)
Greater than or equal to 1.5	and	Greater than or equal to 90	100%
1.0 less than 1.5	or	70 less than 90	75%
Less than 1.0	or	Less than 70	delay

For cycles of PACLitaxel only:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (PACLitaxel)
Greater than or equal to 1.5	and	Greater than or equal to 90	175 mg/m^2
1.0 less than 1.5	or	70 less than 90	150 mg/m^2
Less than 1.0	or	Less than 70	delay

2. **Renal dysfunction:** Dose modification may be required for cyclophosphamide. Refer to Cancer Drug Manual.
3. **Hepatic dysfunction:** Dose modification required for DOXOrubicin and for PACLitaxel. Refer to Cancer Drug Manual.
4. **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 7-10 days
5. **Neuropathy:** Dose modification or discontinuation for PACLitaxel may be required. Refer to Cancer Drug Manual.

6. **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:
Mackey JR, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol 2008;15(1): 24-31.

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

PRECAUTIONS:

1. **Febrile Neutropenia**: Risk of febrile neutropenia is 10 to 20%. If a patient has additional risk factors outlined in Eligibility Note above, risk of febrile neutropenia may be considered to be greater than 20%; consider prophylactic filgrastim per discretion of the treating physician. Febrile neutropenia can result in serious patient harm, treatment delays, and hospitalization. Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Extravasation**: DOXOrubicin and PACLitaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment recommended if lifelong dose of 450 mg/m^2 to be exceeded. Refer to Cancer Drug Manual.

4. **Hypersensitivity**: Reactions are common with PACLitaxel. Refer to BC Cancer SCDRUGRX.

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

6. **CNS Metastases on Adjuvant Trastuzumab:** Patients with HER-2/neu over-expression have been observed to have a higher than usual risk of developing CNS metastases. The CNS is a sanctuary site, unreached by most adjuvant systemic agents. There is little or no data to guide physicians in the circumstance of a patient developing isolated CNS metastasis while on adjuvant therapy with a trastuzumab-containing regimen. Aggressive local therapy (whole brain radiation with or without surgical resection) has resulted in some durable remissions. The Breast Tumour Group supports resection of metastases and CNS radiation if feasible for patients who develop limited and isolated CNS metastases while on an adjuvant trastuzumab regimen. A metastatic survey should be done to determine the best systemic management plan. Completion of the adjuvant course of trastuzumab, or continuing beyond the adjuvant course (changing to BRAVTR regimen) due to concern for occult systemic metastases is at the discretion of the treating oncologist and dependent on the individual circumstances.

7. **A possible interaction between 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 every 2 weeks 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.

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. Henderson IC, Beryy D, Demetri G, Cirrincione C et al. Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (PTS) with node-positive primary breast cancer (BC). Proc Am Soc Clin Oncol 1998;17:101a.
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.