BC Cancer Protocol Summary for Alternative Neoadjuvant or Adjuvant Therapy for Breast Cancer using PACLitaxel NAB (ABRAXANE), CARBOplatin and Trastuzumab

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

ELIGIBILITY:
Patients must have:
- Previous severe hypersensitivity reaction or anaphylaxis to DOCEtaxel that is not manageable despite use of premedications,
  or
- Previous moderate DOCEtaxel hypersensitivity reaction that cannot be managed by premedications due to a strong contraindication to high dose steroids, such as poorly controlled diabetes,
- Been treated with curative intent breast cancer protocol BRAJDCARBT, and
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory

Patients should have:
- Adequate hematological, renal and hepatic function
- No clinically significant cardiac disease

EXCLUSIONS:
Patients must not have:
- Severe hepatic dysfunction contraindicating PACLitaxel NAB (ABRAXANE)

CAUTIONS:
- Greater than or equal to grade 2 sensory or motor neuropathy
- 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, platelets, bilirubin, ALT, GGT, LDH, alkaline phosphatase, creatinine
- Before each treatment: CBC & Diff, platelets, creatinine, bilirubin, ALT
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab and every 3-4 months during the 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: GGT, alkaline phosphatase, urea, MUGA scan or echocardiogram

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg	Loading dose not required (first dose already given in the previous trastuzumab-containing protocol) ▪ IV in 250 mL NS over 1 hour on the second (overall) 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.*
PACLitaxel NAB (ABRAXANE)	260 mg/m^2	IV over 30 minutes**
CARBOplatin	Dose = AUC 6 x (GFR + 25)	In 100 to 250 mL NS over 30 minutes

* Observation period not required after 3 consecutive treatments with no reaction
in empty sterile bags and tubing with **15 micron filter; no specific material required for bag or tubing

Repeat every 21 days to complete total number of cycles in original BRAJDCARBT protocol, followed by single-agent trastuzumab to complete total 51 weeks or 17 doses (see BC Cancer protocol **BRAJTR**)

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).

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:

Doses are adjusted based on Day 1 counts. No dose reduction for nadir counts**. No reduction of trastuzumab dose for hematologic toxicity.**

1. Hematological PACLitaxel NAB and CARBOplatin

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose PACLitaxel NAB	Dose CARBOplatin	Filgrastim (G-CSF) Option
greater than or equal to 1.5	and	greater than or equal to 100	100% (260 mg/m^2)	100%	
1.0 to less than 1.5	and	greater than or equal to 100	220 mg/m^2	75%	100% regimen with G-CSF 300 mcg subcutaneously daily on Days 3-10 (adjust as needed)
less than 1.0	or	less than 100	delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then consider giving 220 mg/m^2	delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 75%	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 100% regimen with filgrastim 300 mcg subcutaneously daily on Days 3-10 (adjust as needed)

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

2. Febrile Neutropenia

Event	PACLitaxel NAB (ABRAXANE) Dose	CARBOplatin Dose Reduction Option	Filgrastim (G-CSF) Option
1st episode	Delay until recovery (ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 100 x 10^9/L), then dose reduce to 220 mg/m^{2**}	75% of previous cycle dose if Day 1 ANC greater than or equal to 1.5 and platelets greater than or equal to 100	100% regimen with filgrastim 300 mcg subcut daily on Days 3-10 (adjust as needed)
2nd episode	Delay until recovery (ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 100 x 10^9/L), then dose reduce to 180 mg/m^{2**}	50% of original cycle dose if Day 1 ANC greater than or equal to 1.5 and platelets greater than or equal to 100	75% regimen with filgrastim 300 mcg subcut daily on Days 3-10 (adjust as needed)
3rd episode	Discontinue protocol or switch to Filgrastim (G-CSF) Option	Discontinue protocol or switch to Filgrastim (G-CSF) Option	50% regimen with filgrastim 300 mcg subcut daily on Days 3-10 (adjust as needed)
4th episode	N/A	N/A	Discontinue protocol

**Dose reductions should be maintained for subsequent cycles and not re-escalated

3. 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 to 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.

4. Hepatic Dysfunction

ALT or AST		Bilirubin	PACLitaxel NAB
Less than or equal to 10 x ULN	and	Greater than 1 to less than or equal to 1.5 x ULN	100%
Less than or equal to 10 x ULN	and/or	Greater than 1.5 to less than or equal to 5 x ULN	80%*
Greater than 10 x ULN	or	Greater than 5 x ULN	Hold

*may re-escalate dose if hepatic function normalizes and reduced dose is tolerated for at least 2 cycles

5. **Renal dysfunction**: If significant increase (greater than 20% or rises above the upper limit of normal) in creatinine, recheck/recalculate GFR and recalculate CARBOplatin dose using new GFR.
   No modification is required for PACLitaxel NAB in mild to moderate renal impairment. PACLitaxel NAB has not been studied in patients with creatinine clearance less than 30 mL/min.

6. Sensory Neuropathy– PACLitaxel NAB

Grade	Toxicity	Dose – 1st Occurrence	Dose – 2nd Occurrence
1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Maintain dose	Maintain dose
2	Sensory alteration or paresthesia (including tingling) but not interfering with function, but not interfering with ADL	Maintain dose	Maintain dose
3	Sensory alteration or paresthesia interfering with ADL	Reduce dose to 220 mg/m^{2**} Consider holding treatment until resolved to grade 2	Reduce dose to 180 mg/m^{2**} Consider holding treatment until resolved to grade 2
4	Disabling	Hold treatment until resolved to grade 2, then reduce dose to 220 mg/m^{2**} or discontinue further treatment at the discretion of physician	Hold treatment until resolved to grade 2, then reduce dose to 180 mg/m^{2**} or discontinue further treatment at the discretion of physician

**Dose reductions should be maintained for subsequent cycles and not re-escalated.

7. **Arthralgia and/or myalgia:** If arthralgia and/or myalgia from PACLitaxel NAB 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 NAB
   - 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 NAB doses to 220 mg/m^2.

8. **Treatment Interruptions –** Trastuzumab

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

PRECAUTIONS:

1. An albumin form of PACLitaxel may substantially affect a drug's functional properties relative to those of drug in solution. **Do not** substitute with or for other PACLitaxel formulations.
2. **Extravasation**: PACLitaxel NAB causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Hypersensitivity:** Reactions to CARBOplatin may occur. Refer to BC Cancer Hypersensitivity Guidelines.
5. **Cardiac toxicity** has been reported rarely while patients receive PACLitaxel NAB. Severe cardiovascular events (3%), including chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension.
6. **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.
7. **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.

8. **Drug interactions:** PACLitaxel NAB is metabolized by CYP2C8 and CYP3A4; caution should be exercised when administering with drugs which are CYP2C8 or CYP3A4 inducers or inhibitors.
9. **Theoretical risk of viral disease transmission**, due to human albumin component, is extremely remote.
10. **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 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:

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2. Gianni L, Mansutti M, Anton A, et al. Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer-The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial: A Randomized Phase 3 Clinical Trial. JAMA Oncol. 2018 Mar 1;4(3):302-308.
3. Untch M, Jackisch C, Schneeweiss A, et al. German Breast Group (GBG); Arbeitsgemeinschaft Gynäkologische Onkologie—Breast (AGO-B) Investigators. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016 Mar;17(3):345-356.
4. Yuan Y, Lee JS, Yost SE, et al. Phase II Trial of Neoadjuvant Carboplatin and Nab-Paclitaxel in Patients with Triple-Negative Breast Cancer. Oncologist. 2021 Mar;26(3):e382-e393.
5. Brufsky A. *nab*-Paclitaxel for the treatment of breast cancer: an update across treatment settings. Exp Hematol Oncol. 2017 Mar 22;6:7.