BC Cancer Protocol Summary for Alternative NEOAdjuvant Therapy for Breast Cancer using Dose Dense Therapy: PACLitaxel NAB (ABRAXANE) followed by DOXOrubicin and Cyclophosphamide

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

ELIGIBILITY:

Patients must have:

- Previous severe hypersensitivity reaction or anaphylaxis to PACLitaxel that is not manageable despite use of premedications,
  or
- Previous moderate PACLitaxel hypersensitivity reaction that cannot be managed by premedications due to a strong contraindication to high dose steroids, such as poorly controlled diabetes, and
- Been treated with curative intent breast cancer protocol BRLATACG

Note: Filgrastim (G-CSF) is not covered as a benefit at BC Cancer

EXCLUSIONS:

Patients must not have:

- Congestive heart failure (LVEF less than 45%) or other significant heart disease
- Severe hepatic dysfunction contraindicating PACLitaxel NAB (ABRAXANE) or DOXOrubicin
- Known hypersensitivity to E. coli derived products

CAUTIONS:

- Greater than or equal to grade 2 sensory or motor neuropathy

TESTS:

- Baseline: CBC & Diff, total bilirubin, ALT, GGT, LDH, alkaline phosphatase, creatinine
- For the cycles of PACLitaxel NAB, before each treatment: CBC & Diff, total bilirubin, ALT, creatinine
- For the cycles of DOXOrubicin and cyclophosphamide, before each treatment: CBC & Diff
- If clinically indicated: GGT, alkaline phosphatase, urea, MUGA scan or echocardiogram
- For the cycles of DOXOrubicin and cyclophosphamide, if clinically indicated: ALT, total bilirubin, creatinine

PREMEDICATIONS:

- For the cycles of PACLitaxel NAB: Additional anti-emetics not usually required
- For the cycles of DOXOrubicin and cyclophosphamide: Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel NAB (ABRAXANE)	260 mg/m^2	IV over 30 minutes*

*in empty sterile bags and tubing with **15** micron filter; no specific material required for bag or tubing

- PACLitaxel NAB to be given every 21 days to complete total number of cycles in original BRLATACG protocol, followed by
- Four consecutive cycles of DOXOrubicin and cyclophosphamide to start 21 days after final cycle of PACLitaxel NAB

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	60 mg/m²	IV push
cyclophosphamide	600 mg/m²	IV in NS 100 to 250 mL over 20 minutes to 1 hour
filgrastim (G-CSF)	5 mcg/kg/day Days 3 to 10 (or adjust as needed**)	subcutaneous

** reduce filgrastim treatment duration if ANC greater than 10 or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

- Repeat every 14 days x 4 cycles.

DOSE MODIFICATIONS:

1. **Hematological**

For the cycles of PACLitaxel NAB only:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.5	and	greater than or equal to 100	100% (260 mg/m^2)
1.0 to less than 1.5	and	greater than or equal to 100	220 mg/m^2
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

For cycles of DOXOrubicin and cyclophosphamide only (for Day 1 counts):

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (all drugs)
Greater than or equal to 1.0	and	Greater than or equal to 100	100%
Less than 1.0	and	Greater than or equal to 100	delay for 1 week (or longer if needed), then give 100% dose if ANC greater than 1 and platelets greater than or equal to 100. Give filgrastim days 3 to 13 for remaining cycles.
Greater than or equal to 1.0	and	Less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1 and platelets greater than or equal to 100
Less than or equal to 1.0	and	Less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1 and platelets greater than or equal to 100

2. Febrile Neutropenia:

PACLitaxel NAB

	1st Occurrence	2nd Occurrence
Febrile Neutropenia	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**}**	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**}**

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

DOXOrubicin and cyclophosphamide: Consider 75% of dose for current and subsequent cycles**.**

3. Hepatic Dysfunction

PACLitaxel NAB

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

DOXOrubicin:

ALT or AST		Bilirubin (micromol/L)	Dose
2 to 3 x ULN		-	75%
greater than 3 x ULN	or	20 to 51	50%
-		51 to 85	25%
-		greater than 85	Do not administer

4. **Renal dysfunction**: 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.
   Dose modification may be required for cyclophosphamide. Refer to BC Cancer Drug Manual.

5. **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.

3. **<u>Arthralgia and/or myalgia</u>:** 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.

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**: DOXOrubicin and PACLitaxel NAB cause pain and tissue necrosis (rarely for PACLitaxel NAB) if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Febrile Neutropenia**: Risk of febrile neutropenia is greater than 20% without the use of filgrastim. Mandatory filgrastim reduces the risk of febrile neutropenia. Febrile neutropenia can result in patient harm, treatment delays, and hospitalization. Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **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.
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. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution in patients with cardiac dysfunction. Cardiac assessment recommended once cumulative dose reaches 300 mg/m^2 (see BC Cancer Drug Manual).
7. **Theoretical risk of viral disease transmission**, due to human albumin component, is extremely remote.

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.