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

***Protocol Code**:*	*BRLAPNAC*
***Tumour Group**:*	*Breast*
***Contact Physician**:*	*Dr. Angela Chan*

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 BRLATWAC

Patients should have:
- Adequate hematological, renal and hepatic function

EXCLUSIONS:
Patients must not have:
- Severe cardiovascular disease with LVEF less than 45%
- Severe hepatic dysfunction contraindicating PACLitaxel NAB (ABRAXANE) or DOXOrubicin

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

TESTS:
- Baseline: CBC & diff, platelets, bilirubin, ALT, GGT, LDH, alkaline phosphatase, creatinine
- Before each treatment: CBC & diff, platelets
- If clinically indicated: bilirubin, ALT, GGT, alkaline phosphatase, urea, creatinine, MUGA scan or echocardiogram

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)

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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 BRLATWAC 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 100 to 250 mL NS over 20 min to 1 hour

- Repeat every 21 days for 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

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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 to less than 1.5	or	70 to less than 90	75%
less than 1.0	or	less than 70	delay

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

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

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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.

6. **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.

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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 if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **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. Angela Chan or tumour group delegate at 604-877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References

1. Sánchez-Muñoz A, Jiménez B, García-Tapiador A, et al. Cross-sensitivity between taxanes in patients with breast cancer. Clin Transl Oncol. 2011 Dec;13(12):904-6.
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.
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5. Brufsky A. *nab*-Paclitaxel for the treatment of breast cancer: an update across treatment settings. Exp Hematol Oncol. 2017 Mar 22;6:7.

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