Regimen Monograph

A - Regimen Name

PACL(W) Regimen
PACLitaxel (weekly)

PACL(W)+TRAS Regimen
PACLitaxel (weekly)-Trastuzumab

Disease Site	Breast
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For the treatment of metastatic breast cancer
Supplementary Public Funding	**trastuzumab** New Drug Funding Program (Trastuzumab (Biosimilar) in combination with Chemotherapy - Metastatic Breast Cancer) (NDFP Website)

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trastuzumab
New Drug Funding Program (Trastuzumab (Biosimilar) - Second Line - Metastatic Breast Cancer)

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B - Drug Regimen

PACLitaxel	80 mg /m²	IV	Days 1, 8, 15

For patients with HER2 positive tumours, trastuzumab may be given concurrently with paclitaxel and then as a single agent

trastuzumab	8 mg /kg	IV loading dose	Day 1, cycle 1 only
THEN,			
trastuzumab	6 mg /kg	IV maintenance dose	Every 21 days

Alternative trastuzumab schedule:

trastuzumab	4 mg /kg	IV loading dose	Day 1, cycle 1 only
THEN,			
trastuzumab	2 mg /kg	IV maintenance dose	Weekly (Q7 Days)

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C - Cycle Frequency

Paclitaxel: REPEAT EVERY 28 DAYS until disease progression or unacceptable toxicity.

Q3 Weekly or Weekly Trastuzumab: See TRAS (Breast - Advanced) regimen for details.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Paclitaxel Pre-medications* (prophylaxis for infusion reaction):

To be given 30-60 minutes prior to paclitaxel infusion.

- Dexamethasone 10 mg IV, starting in cycle 1
- Diphenhydramine 25-50 mg IV/PO
- Ranitidine 50 mg IV OR Famotidine 20 mg IV

* Consider **discontinuing** pre-medications for paclitaxel if there was no IR in the first 2 doses.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

See TRAS (Breast - Advanced) regimen for details on trastuzumab dose modifications.

Dosage with toxicity

Dose levels: 80 mg/m², 70 mg/m², 60 mg/m². Dose re-escalations are not allowed. Discontinue treatment if toxicity recurs after 2 dose reductions.

Toxicity (Grade or Counts x 10^9/L)	Paclitaxel dose
ANC < 1.5 and/or Platelets < 100	Delay[1]
ANC ≤ 0.8 and/or Platelets ≤ 50	Delay[1]; ↓ 1 level for next dose
Grade 2 neurotoxicity	↓ 1 level

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Other Grade 2-3 non-hematological[2, 3] or grade 3 neurotoxicity	Delay[1]; ↓ 1 level
Grade 4 non-hematological[3]; more than 2 weeks delay or more than 2 dose reductions	Discontinue

[1] Delay for up to 2 weeks. Start day 1 of cycle when non-hematologic toxicities recover to ≤ grade 1, platelets ≥ 100 x 10^9 /L, and ANC ≥ 1.5 x 10^9 /L; reduce dose as per table.

[2] Except alopecia, fatigue and nausea. Appropriate symptom management should be provided for vomiting, diarrhea, constipation; dose modifications may not be necessary.

[3] Except infusion reactions. See **Management of Infusion Reactions** table below for dose modifications pertaining to infusion reactions.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Paclitaxel:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• Consider re-challenge with pre-medications and at a reduced infusion rate. • After 2 subsequent IRs, consider replacing with a different taxane. Give intensified pre-medications and reduce the infusion rate. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary. • There is insufficient evidence to recommend substitution with another taxane at re-challenge. • High cross-reactivity rates have been reported.

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Hepatic Impairment

For paclitaxel, patients with hepatic impairment may be at risk of toxicity, especially myelosuppression (see table for suggested dosage adjustment). No dosage adjustment required for trastuzumab.

Bilirubin and/or AST/ALT	**Dose (mg/m^2)**
2-4 x ULN	60
>4 x ULN	40 or omit

Renal Impairment

No adjustment required for paclitaxel, but may consider for patients with HIV-AIDS if creatinine ≥ 2 x ULN. No dosage adjustment required for trastuzumab.

Dosage in the Elderly

No adjustment required. Elderly patients are more at risk for severe toxicity with paclitaxel and increased risk for cardiac dysfunction and myelosuppression with trastuzumab.

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F - Adverse Effects

Refer to PACLitaxel (± trastuzumab) drug monograph(s) for additional details of adverse effects.

See TRAS (Breast - Advanced) regimen for details on trastuzumab adverse effects.

Paclitaxel:

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Alopecia (may be permanent) • Musculoskeletal pain (may be severe) • Neuropathy (may be severe, includes cranial nerves and autonomic)	• Diarrhea • Nausea/vomiting • Myelosuppression +/- infection and bleeding (may be severe) • Hypersensitivity (may be severe)	• Hypotension • ECG changes • Mucositis • Edema • Fatigue • ↑ LFTs (may be severe)	• Arrhythmia • Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Injection site reactions • Rash • GI obstruction • GI perforation • Pancreatitis • Secondary malignancy • Encephalopathy • Seizures • Cystoid macular edema • Pneumonitis • Typhlitis • Radiation recall

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G - Interactions

Refer to PACLitaxel (± trastuzumab) drug monograph(s) for additional details.

See TRAS (Breast - Advanced) regimen for details on trastuzumab drug interactions.

- Caution with concurrent use of paclitaxel with CYP2C8/3A4 substrates, inhibitors and inducers.

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H - Drug Administration and Special Precautions

Refer to PACLitaxel (± trastuzumab) drug monograph(s) for additional details.

See TRAS (Breast - Advanced) regimen for details on trastuzumab Drug Administration and Special Precautions.

Paclitaxel:

Administration

- In order to minimize patients' exposure to DEHP leaching from PVC bags or sets, use polyolefin or polypropylene infusion bags and polyethylene-lined administration sets (with a 0.22 micron in-line filter).
- Dilute in Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL and infuse over 3 hours.
- For weekly dosing, may be infused over 1 hour - mix in 250mL bag as above (not approved by manufacturer).
- Extended infusion of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.
- Excessive shaking, agitation, or vibration may induce precipitation and should be avoided.
- Precipitation may rarely occur with infusions longer than 3 hours.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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Contraindications:

- Patients with a history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil)
- Patients with severe baseline neutropenia (<1.5 x 10^9/L; < 1 x 10^9/L for patients with AIDS-related Kaposi's)

Other Warning/Precautions:

- Paclitaxel contains ethanol, and is administered with agents such as antihistamines which cause drowsiness. Patients should be cautioned regarding driving and the use of machinery.

Pregnancy/Lactation:

- Paclitaxel is not recommended for use in pregnancy.
- Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility effects: Yes

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I - Recommended Clinical Monitoring

Also refer to TRAS (Breast - Advanced) regimen for details

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline and at each visit
- Liver and renal function tests; Baseline and at each visit
- Blood pressure and pulse rate monitoring during infusion. Cardiac monitoring with prior arrhythmia; Baseline and as clinically indicated

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- Clinical toxicity assessment of bleeding, infection, musculoskeletal effects, neurologic (sensory) effects, hypersensitivity and flu-like symptoms; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- CBC; As clinically indicated
- Liver function tests; As clinically indicated
- Renal function tests (AIDS-related Kaposi's sarcoma); Baseline and before each dose

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J - Administrative Information

Approximate Patient Visit

PACL(W)	2 hours
PACL(W)+TRAS	First cycle: 3.5 hours; Subsequent cycles: 2.5 cycles

Pharmacy Workload **(average time per visit)**

PACL(W)	18.663 minutes
PACL(W)+TRAS	27.752 minutes

Nursing Workload **(average time per visit)**

PACL(W)	39.833 minutes
PACL(W)+TRAS	55.667 minutes

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K - References

Paclitaxel drug monograph, Cancer Care Ontario.

Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, With trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of cancer and leukemia group B protocol 9840. J Clin Oncol 2008; 26:1642-9.

Seidman A D, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for

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metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. J Clin Oncol 2001; 19(10): 2587-95.

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M - Disclaimer

Regimen Abstracts

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Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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