Regimen Monograph

A - Regimen Name

PACL(W)+TRAS Regimen

PACLitaxel (weekly)-Trastuzumab

Disease Site	Breast
Intent	Adjuvant
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	Treatment of HER2-positive breast cancer Note: The clinical trial included patients with negative nodes (a single axillary lymph node micrometastasis was allowed) and tumor size < 3 cm.
Supplementary Public Funding	**trastuzumab** New Drug Funding Program (Trastuzumab (Biosimilar) - Adjuvant Treatment for Breast Cancer) (NDFP Website)

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B - Drug Regimen

Note: Different trastuzumab products are **not interchangeable**.

Paclitaxel Weekly for 12 weeks[1]:

PACLitaxel	80 mg /m²	IV (1 hour infusion)	Day 1

Q7 Days

PLUS

Trastuzumab[2] to be given for one year, starting concurrently with Paclitaxel.

Weekly Trastuzumab Schedule - LOADING DOSE:

trastuzumab	4 mg /kg	IV over 90 minutes	Day 1 (week 1)

***THEN*, Weekly Trastuzumab - MAINTENANCE DOSE:**

trastuzumab	2 mg /kg	IV over 30 minutes*	Day 1 (starting week 2)

Q7 Days

OR Alternative Trastuzumab Schedule:

Q21 Day Trastuzumab Schedule - LOADING DOSE:

trastuzumab	8 mg /kg	IV over 90 minutes	Day 1 (Cycle1)

***THEN*, Q21 Day Trastuzumab - MAINTENANCE DOSE:**

trastuzumab	6 mg /kg	IV over 30 minutes*	Day 1 (starting cycle 2)

Q21 Days

*if loading dose was well-tolerated

[1] If a dose of paclitaxel is missed, it should be made up (trastuzumab should be given even if paclitaxel missed). Up to 3 doses can be made up and should be completed within 16 weeks of starting treatment.

[2] In the clinical trial (Tolaney *et al*), patients were given weekly trastuzumab during the paclitaxel phase (x 12 weeks), then they either continued on the weekly schedule or switched to the Q21 day schedule. A repeat loading dose was not needed as long as the trastuzumab monotherapy is started 1 to 3 weeks after the completion of combination therapy.

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C - Cycle Frequency

WEEKLY (Paclitaxel) x 12 doses
unless disease progression or unacceptable toxicity occurs

Trastuzumab is given for one year treatment duration and may start concurrently with paclitaxel treatment.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Febrile Neutropenia Risk: Low

Other Supportive Care:

- Weekly Paclitaxel: Patients should be pretreated with a corticosteroid as well as an antihistamine and a H2 blocker. For example:
  - Dexamethasone 10mg IV 30 minutes before paclitaxel
  - Diphenhydramine 50mg IV 30 minutes before paclitaxel
  - Ranitidine 50mg IV 30 minutes before paclitaxel

- Trastuzumab: Nausea and vomiting are usually symptoms that are related to infusion-associated reactions. To prevent recurrence of infusion-associated reactions, acetaminophen and diphenhydramine may be given as pre-medication. Refer to Trastuzumab drug monograph for full details.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Paclitaxel:

- Patients should not be treated until neutrophil ≥ 0.8 x 10^9/L and platelet counts ≥ 100 x 10^9/L.
- If trastuzumab is held or discontinued during paclitaxel treatment, paclitaxel may continue at the discretion of the physician

Suggested dose levels:

Dose level	Dose of Paclitaxel (mg/m^2) per week
ideal starting dose	80
-1	70
-2	60
-3	50
-4	40

- Missed doses should be made up. Once the dose has been decreased, it should not be re-escalated.
- Discontinue treatment if toxicity recurs after 4 dose reductions (or specified in the table below).

Worst Toxicity Type / Counts x 10^9/L in the Previous Cycle	Paclitaxel (% previous dose)
Febrile Neutropenia; Infection with or without neutropenia; Thrombocytopenic bleeding; Grade 4 ANC ≥7 days	First occurrence: May consider GCSF (if neutropenia) and restart at previous dose 2nd occurrence: *Give with GCSF (if neutropenia) and restart by ↓ 1 dose level 3rd occurrence: *Give with GCSF (if neutropenia) and restart by ↓ 1 dose level 4th occurrence: *Discontinue paclitaxel
Grade 3 neurotoxicity	Hold*; restart at ↓ 1 dose level
Worsening neurotoxicity (even if grade 2)	may consider ↓ 1 dose level
Grade 3 nausea/vomiting	Hold until ≤ grade 2; restart at 80% dose; Discontinue if grade 3 recurs despite dose reduction
Grade 2 mucositis or diarrhea on day of treatment	Hold until ≤ grade 1; restart at same dose
≤ Grade 3 mucositis or diarrhea	Hold until ≤ grade 1; restart at ↓ 1 dose level (lowest dose level = 60 mg/m^2)
Grade 3 related organ	Hold*, then 80%
Grade 4 related organ, neurotoxicity	Discontinue
*Do not retreat until toxicity has recovered to ≤ grade 2 (or indicated in table), platelets ≥ 100 x 10^9/L, and ANC ≥ 0.8 x 10^9/L. Discontinue paclitaxel if delay for > 21 days (or > 14 days for neurotoxicity). Missed paclitaxel doses (up to 3) can be made up; all paclitaxel doses must be given within 16 weeks of starting treatment.	

Trastuzumab:

- No dose adjustment required for hematological toxicity.
- Trastuzumab may be continued if paclitaxel is delayed (other than for cardiotoxicity or severe hypersensitivity reactions that occurred when both drugs were given).
- For maintenance treatment, if a patient has not had a dose for ≥ 28 days, a loading dose should be given (Tolaney *et al*).

Cardiotoxicity:

Relationship of LVEF to Lower Limit of Normal (LLN)	Trastuzumab dose modification based on asymptomatic LVEF decrease from baseline		
	< 10 percentage points	**10-15 percentage points**	**≥ 16 percentage points**
Within facility's normal limits	Continue	Continue	**Hold** and repeat MUGA/ECHO after 4 weeks
1-5% below LLN	Continue [1]	**Hold** and repeat MUGA/ECHO after 4 weeks [1, 2]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]
≥ 6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks [3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]

[1] Consider cardiac assessment and starting ACEI therapy

[2] After 2 holds, consider permanent trastuzumab discontinuation

[3] Start ACEI therapy and refer to cardiologist

Management of Hypersensitivity:

Toxicity	Action
Mild hypersensitivity reaction (Grade 1): flushing, rash, pruritus	Consider ↓ infusion rate; complete infusion and observe patient. Consider premedication for next infusion.
Moderate hypersensitivity reaction (Grade 2): moderate rash, flushing, mild dyspnea, chest discomfort	Hold and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate; complete infusion at ↓ rate if possible. Use premedication for next infusion. May resume infusion at a rate of 10% of original rate for 15 minutes, then at 25% of original rate for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete.
Severe hypersensitivity reaction (Grade 3): hypotension, angioedema, respiratory distress, generalized urticaria	Hold and manage symptoms aggressively with beta-agonists, antihistamines, antipyretics, and/or corticosteroids. Re-challenge at a slower rate, only after premedication with at least a corticosteroid and antihistamine.

Hepatic Impairment

Trastuzumab: No adjustment required.

Paclitaxel: Caution and dose reduction advised in patients with moderate to severe hepatic impairment. Patients with hepatic impairment may be at risk of toxicity, especially severe myelosuppression. Suggested are:

Bilirubin and/or AST/ALT	Paclitaxel Dose
1.5-3 x ULN	Hold for 1 week; restart at same dose if ≤ grade 1; restart by ↓ 1 dose level if remains at grade 2 (may re-escalate if recover to ≤ grade 1.)
>3 x ULN	Hold; then restart with 50% dose or discontinue

Renal Impairment

Trastuzumab and Paclitaxel: No adjustment required.

Dosage in the Elderly

No adjustment of paclitaxel required, but elderly patients are more at risk for severe toxicity.

No adjustment of trastuzumab is required; the risk of cardiac dysfunction and myelosuppression may be increased in elderly patients. The reported trials did not determine differences in efficacy between patients > 65 years versus younger patients.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Alopecia • Peripheral neuropathy (may be severe) • Musculoskeletal pain	• Nausea, vomiting • Infusion-related reaction (may be severe) • Myelosuppression ± infection, bleeding (may be severe) • Diarrhea	• ↑ in LFTs (may be severe) • Edema • Mucositis • Fatigue • ECG changes • Injection site reaction	• Arrhythmia • Arterial thromboembolism • Cardiotoxicity • Venous thromboembolism • GI perforation, obstruction • AML, MDS • Pneumonitis • Pancreatitis • Rash • Renal failure • Radiation recall reaction • Secondary malignancies • Encephalopathy • Seizure • Eye disorders (cystoid macular edema, optic nerve disorder

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G - Interactions

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

- Monitor INR in patients receiving warfarin; warfarin dosage adjustment may be required.

- Concurrent use with radiation may increase the risk of radiation pneumonitis
- Caution and monitor with CYP3A4 and CYP 2C8 inducers , inhibitors, and substrates
- Avoid concomitant use of cardiotoxic drugs as additive effects may occur

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H - Drug Administration and Special Precautions

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

Note: Different trastuzumab products are **not interchangeable**.

Administration

Paclitaxel:

- 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 250-500 mL Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL.
- For weekly dosing, infuse over 1 hour
- Excessive shaking, agitation, or vibration may induce precipitation and should be avoided.

Trastuzumab:

- **NOTE:** Herceptin® (trastuzumab) and Kadcyla® (trastuzumab emtansine) are **NON-INTERCHANAGEABLE**. There have been fatal reports where the incorrect trastuzumab product was administered to patients with breast cancer in the clinical trials setting.
- Mix in 250 mL bag NS. Do not use D5W as it causes protein aggregation. Do not shake.
- Infuse loading dose IV over 90 minutes; subsequent infusions may be given over 30 minutes if the initial loading dose is well-tolerated.
- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.
- Should not be mixed or diluted with other drugs.
- Diluent supplied - Bacteriostatic Water for Injection (BWFI) - contains benzyl alcohol 1.1%; if patient is hypersensitive to benzyl alcohol, may reconstitute with Sterile Water for Injection, but must be used immediately and discard unused portion.
- Solution reconstituted with the supplied BWFI is stable up to 28 days refrigerated.
- Do not freeze the reconstituted solution.

Contraindications:

- Patients with a history of severe hypersensitivity reactions to paclitaxe, trastuzumab, drugs formulated in Cremophor EL (polyethoxylated castor oil), Chinese Hamster Ovary (CHO) cell

proteins, or any components of these products
- Patients with severe baseline neutropenia
- Trastuzumab should only be used in patients whose tumours overexpress HER

Other Warnings/Precautions:

- Severe arrhythmias may occur during infusion; patients should be appropriately managed and undergo continuous ECG monitoring during subsequent infusions. Congestive heart failure (including LVEF decrease) has been reported in patients who have received other chemotherapy agents, especially anthracyclines.
- 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.
- The risk of cardiotoxicity must be weighed against the potential benefits of treatment, especially in older patients, patients with pre-existing cardiac disease (including LVEF < 55%) and patients who have had prior cardiotoxic therapy. Note: in the adjuvant trials, patients with cardiac risk factors were excluded from the trials.
- Exercise caution in patients with pre-existing pulmonary disease or patients with extensive pulmonary tumour involvement, as they may experience more severe lung toxicities.
- Use with caution before or after anthracyclines (for up to 24 weeks after trastuzumab discontinuation due to long half-life).
- Life-threatening infusion-related reactions associated with the administration of trastuzumab may occur. See Adverse Effects for recommended precautions, monitoring, and treatment.

Pregnancy and Lactation:

- Trastuzumab and paclitaxel are not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 7 months after the last dose (for women of child-bearing potential).
- Breastfeeding is not recommended.

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I - Recommended Clinical Monitoring

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 before each paclitaxel treatment
- Liver function tests; Baseline and before each cycle
- Blood pressure and pulse rate monitoring during paclitaxel infusion, cardiac monitoring with prior arrhythmia
- Cardiac assessment, including evaluation of left ventricular function (Echocardiogram or MUGA scan); more frequent with asymptomatic reductions in

LVEF; baseline, q3 months during treatment, then q6 months after trastuzumab discontinuation x2 years (and annually up to 5 years after last trastuzumab dose in adjuvant breast cancer patients who received anthracyclines), also as clinically indicated;
- Clinical assessment of bleeding, infection, diarrhea, musculoskeletal, neurologic (sensory), infusion reactions, flu-like symptoms, cardiotoxicity, lung toxicity; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Renal function tests; baseline and as indicated

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J - Administrative Information

Approximate Patient Visit	First cycle: 3.5 hours; Subsequent cycles: 2.5 cycles
Pharmacy Workload (average time per visit)	27.752 minutes
Nursing Workload (average time per visit)	55.667 minutes

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K - References

Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015 Jan 8;372(2):134-41.

Paclitaxel and trastuzumab drug monographs, Cancer Care Ontario.

February 2022 Removed trastuzumab EBP forms

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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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