Regimen Monograph

A - Regimen Name

AC-PACL(W) Regimen

ADRIAMYCIN ® (DOXOrubicin)-Cyclophosphamide then PACLitaxel Weekly

AC-PACL(W)+TRAS Regimen

ADRIAMYCIN ® (DOXOrubicin)-Cyclophosphamide then PACLitaxel Weekly and Trastuzumab

Disease Site	Breast
Intent	Neoadjuvant 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	Neo-adjuvant or adjuvant treatment for node-positive and high risk node-negative early breast cancer. Trastuzumab may be used concurrently with paclitaxel or after completion of paclitaxel in HER-2 positive breast cancer.
Supplementary Public Funding	**trastuzumab** New Drug Funding Program (Trastuzumab (Biosimilar) - Adjuvant Treatment

for Breast Cancer)

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B - Drug Regimen

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

AC: (x 4 cycles)

DOXOrubicin	60 mg /m²	IV	Day 1
cyclophosphamide	600 mg /m²	IV	Day 1

Repeat Every 21 Days

THEN

PACLITAXEL Weekly: (x 12 doses)

PACLitaxel	80 mg /m²	IV	Day 1

Repeat Every 7 Days

For patients with HER2 positive tumours, **Trastuzumab** may be given for one year, starting concurrently with paclitaxel or after 12 weekly cycles of paclitaxel:

trastuzumab	8 mg /kg	IV loading dose	Day 1, cycle 1 only

THEN,

trastuzumab	6 mg /kg	IV maintenance dose	Every 21 Days

Alternative chemotherapy schedule:

AC: (x 4 cycles)

DOXOrubicin	60 mg /m²	IV	Day 1
cyclophosphamide	600 mg /m²	IV	Day 1

Repeat Every 14 Days

THEN

PACLITAXEL Weekly: (x 12 doses)

PACLitaxel	80 mg /m²	IV	Day 1

Repeat Every 7 Days

Alternative Trastuzumab schedule:

For patients with HER2 positive tumours, **Trastuzumab** may be given for one year, starting concurrently with paclitaxel or after 12 weekly cycles of paclitaxel:

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

AC X 4 cycles then weekly Paclitaxel (Taxol®) X 12 doses

Q3 Weeks or Weekly Trastuzumab**:** Refer to TRAS (Breast - Adjuvant) regimen for details.

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (AC)
Low (Paclitaxel)

Febrile Neutropenia Risk: Low

AC(Q3W)-PACL(W)

High
AC(Q2W)-PACL(W): Use G-CSF prophylaxis for patients at high risk of febrile neutropenia. See G-CSF recommendations.

Other Supportive Care:

• 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

Also refer to CCO Antiemetic Summary

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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 are in use at some centres.

Dosage with toxicity

Hematologic Toxicities: See Appendix 6 for general recommendations.

Suggested Dose Levels:
Doxorubicin: 60 mg/m², 45 mg/m², 30 mg/m²
Cyclophosphamide: 600 mg/m², 450 mg/m², 300 mg/m²
Paclitaxel: 80 mg/m², 60 mg/m², 40 mg/m²

Toxicity Type / Counts x 10^9/L		**Toxicity Type / Counts x 10^9/L**	**Doxorubicin***	**Cyclophosphamide***	**Paclitaxel***
ANC < 1.5	Or	Platelet < 100	Hold*	Hold*	Hold*
Febrile Neutropenia	Or	ANC < 0.5	Hold* and ↓ 1 dose level or GCSF	Hold* and ↓ 1 dose level or GCSF	Hold* and ↓ 1 dose level or GCSF
Grade 3 neurotoxicity			100%	100%	↓ 1 dose level *
Other Grade 3 non-hematologic			↓ 1 dose level*	↓ 1 dose level*	↓ 1 dose level*
Grade 4 non-hematologic			Discontinue	Discontinue	Discontinue
* Major organ toxicity should have recovered to ≤ grade 2, ANC to ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L prior to retreatment.					

Hepatic Impairment

Bilirubin *	**Doxorubicin (% previous dose)**	**Cyclophosphamide**	**Paclitaxel (% previous dose)**
1-2 X ULN	50%	No adjustment required	Caution
2-4 X ULN	25%	Caution	75%
> 4 X ULN	OMIT	Caution	50% or OMIT

*Consider dose reduction for doxorubicin and paclitaxel for severe increase(s) in transaminases.

Renal Impairment

Creatinine Clearance (mL/min)	Doxorubicin	Cyclophosphamide (% previous dose)	Paclitaxel
>30 – 50	No adjustment required	100%	No adjustment required
10 – 30		50 – 75%	
<10		50% or OMIT	

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F - Adverse Effects

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

Refer to trastuzumab drug monograph for adverse effect details (not listed below).

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Nausea and vomiting • Myelosuppression ± infection • Fatigue • Stomatitis and diarrhea • Neurotoxicity • Hypersensitivity reactions (paclitaxel) • Myalgia and arthralgia • Alopecia • Cystitis • Cardiotoxicity (may be severe) • Increased LFTs, bilirubin • Rash (may be severe)	• Pneumonitis, pulmonary fibrosis • SIADH • DIC, hemolytic uremic syndrome, renal failure • Secondary leukemia • Venous/arterial thromboembolism • Abnormal ECG, cardiac failure, acute MI • Pancreatitis, GI perforation, typhlitis, obstruction

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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

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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 cycle
- Liver function tests; baseline and before each cycle
- Renal function tests and urinalysis; baseline and before each cycle
- Cardiac function tests (echocardiogram or MUGA scan) and examination especially with risk factors (including prior therapy with epirubicin, mitoxantrone, or other cardiotoxic drug), or a cumulative doxorubicin dose of > 450 mg/m^2; baseline and regular
- Blood pressure and pulse rate monitoring during paclitaxel infusion; baseline and as clinically indicated
- Clinical toxicity assessment, including GI toxicity, cardiotoxicity, local toxicity, cystitis, hypersensitivity, neurotoxicity, musculoskeletal effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit

AC-PACL(W)	AC: 1 to 1.5 hours; Paclitaxel: 2 hours
AC-PACL(W)+TRAS	AC: 1 to 1.5 hours; Paclitaxel: 2 hours; TRAS: First cycle - 1.5 hours; Subsequent cycles - 0.5 hour

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

AC-PACL(W)	20.888 minutes
AC-PACL(W)+TRAS	23.31 minutes

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

AC-PACL(W)	51.542 minutes
AC-PACL(W)+TRAS	56.542 minutes

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K - References

Doxorubicin, cyclophosphamide, paclitaxel and trastuzumab drug monographs, Cancer Care Ontario.

Henderson IC, Berry D, Demetri G, Cirrincione C, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003; 21(6): 976-83.

Romond EH, Perex EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. NEJM 2005; 353(16) 1673-84.

Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. NEJM 2008; 358(16): 1663-71.

PEBC Advice Documents or Guidelines

- Optimal Systemic Therapy for Early Female Breast Cancer

February 2022 Removed trastuzumab EBP forms; updated Rationale and uses section

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

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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