Regimen Monograph

A - Regimen Name

AC-PACL(DD) Regimen

ADRIAMYCIN ® (DOXOrubicin)-Cyclophosphamide then PACLitaxel (Dose Dense)

AC-PACL(DD)+TRAS Regimen

ADRIAMYCIN ® (DOXOrubicin)-Cyclophosphamide then PACLitaxel (Dose Dense) 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

THEN

PACLITAXEL (Taxol®): **(x 4 cycles)**

PACLitaxel	175 mg /m²	IV	Day 1

For patients with HER2 positive tumours, **Trastuzumab** may be given for one year, **starting either concurrently with paclitaxel or after 4 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

Alternate trastuzumab schedule (Every 14 days)*:

Start concurrently with paclitaxel:

trastuzumab*	8 mg /kg	IV loading dose	Day 1, with cycle 1 of paclitaxel
THEN,			
trastuzumab*	4 mg /kg	IV maintenance dose	Every 14 Days, with cycles 2-4 of paclitaxel

Two weeks after cycle 4 of paclitaxel, continue with single agent trastuzumab 6 mg/kg IV q3 weeks. Refer to TRAS regimen.

*Breast Drug Advisory Committee consensus.There may be other clinically appropriate q14 day trastuzumab dosing regimens. Refer to local protocols.

Alternate trastuzumab schedule (Weekly):

Start concurrently with paclitaxel:

trastuzumab	4 mg /kg	IV loading dose	Day 1, with cycle 1 of paclitaxel
THEN,			
trastuzumab	2 mg /kg	IV maintenance dose	Weekly

One week after cycle 4 of paclitaxel, continue with single agent trastuzumab 6 mg/kg IV q3 weeks. Refer to TRAS regimen.

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C - Cycle Frequency

REPEAT EVERY 14 DAYS: AC X 4 cycles then Paclitaxel (Taxol®) X 4 cycles

Trastuzumab: For a usual treatment duration of one year unless limited by cardiotoxicity risk. Refer to TRAS regimen for trastuzumab continuation after AC-PACL(DD).

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (AC)
Low (Paclitaxel)

Febrile Neutropenia Risk: High

Primary prophylaxis with G-CSF is indicated for AC-PACL(DD). Refer to the Febrile neutropenia guideline.

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Pre-medications* (prophylaxis for infusion reaction with paclitaxel):

- Dexamethasone 20 mg PO 12-and 6-hours OR Dexamethasone 20 mg IV 30 minutes pre-infusion†
- Diphenhydramine 25-50 mg IV/PO 30-60 minutes pre-infusion
- Ranitidine 50 mg IV OR Famotidine 20 mg IV 30-60 minutes pre-infusion

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

† Oral and IV dexamethasone are both effective at reducing overall IR rates. Some evidence suggests that oral dexamethasone may be more effective for reducing severe reactions; however, adverse effects and compliance remain a concern.

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E - Dose Modifications

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

Refer to TRAS (Breast - Adjuvant) regimen for details on trastuzumab dose modifications.

Dosage with toxicity

Hematologic Toxicities: See general recommendations.

Toxicity Type / Counts x 10^9/L		Toxicity Type / Counts x 10^9/L	Doxorubicin (% previous dose)	Cyclophosphamide (% previous dose)	Paclitaxel (% previous dose)
ANC <1.5	Or	Platelet < 100	Hold *		
Febrile Neutropenia, or Grade 4 ANC ≥ 7 d	Or	Thrombocytopenic bleeding	Hold * then 75%		
ANC ≥ 1.5	And	Platelet ≥ 100	100%		
Grade 3/4 Neurotoxicity			Not applicable		80%*
Grade 3 related organ			*75% for suspect drug(s). If cardiotoxicity, follow recommendations in doxorubicin and paclitaxel drug monographs.		
Grade 4 related organ			Discontinue		

*Retreat when toxicities have recovered to ≤ grade 2, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.

Hepatic Impairment

Bilirubin		AST/ALT	Cyclophosphamide	Doxorubicin	Paclitaxel
			(% of previous / mg/m^2)		
1-2 x ULN	and/ or	-	100%	50%	100%
2-4 x ULN		2-4 xULN	Caution	25%	135mg/m^2
>4 x ULN		>4 x ULN	Caution	Discontinue	50mg/m^2 or OMIT

Renal Impairment

Creatinine Clearance (mL/min)	Cyclophosphamide	Doxorubicin	Paclitaxel
	(% of previous)		
>30-50	100%	100%	100%
10-30	50-75%	100%	100%
<10	50% or OMIT	100%	100%

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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).

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Alopecia • Myelosuppression ± infection, bleeding (may be severe) • Nausea and vomiting (more likely with AC) • Musculoskeletal pain (more likely with PACL)	• Hypersensitivity reactions (with PACL) • Diarrhea • Neuropathy (may be severe; with PACL)	• Edema • ↑ LFTs (with PACL) • Fatigue • Abdominal pain • Anorexia • Nail changes • ECG changes • Dysguesia • Dizziness • Cystitis (with AC) • Mucositis	• Cardiotoxicity • Secondary leukemia/malignancies • Arterial/Venous Thromboembolism • Pneumonitis • SIADH • DIC, Hemolytic Uremic Syndrome • Rhabdomyolysis • Pancreatitis, GI obstruction, perforation • Radiation Recall • Injection Site reactions • Encephalopathy • Seizures

			• Vasculitis • QTc Prolongation • Optic neuritis • Cystoid macular edema

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G - Interactions

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

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H - Drug Administration and Special Precautions

Refer to DOXOrubicin, cyclophosphamide, filgrastim, 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.

Refer to TRAS (Breast - Adjuvant) regimen for details on trastuzumab clinical monitoring.

Recommended Clinical Monitoring

- Clinical toxicity assessment (including stomatitis, cardiotoxicity, local toxicity, cystitis, hypersensitivity, neuropathy, musculoskeletal, infection or diarrhea); at each visit
- CBC before each cycle
- Baseline and regular liver function tests
- Baseline and regular renal function tests and urinalysis

- Cardiac 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
- 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(DD)	AC: 1 to 1.5 hours; Paclitaxel: 5 hours
AC-PACL(DD)+TRAS	AC: 1 to 1.5 hours; Paclitaxel hours: 5; TRAS: First cycle - 1.5 hours; Subsequent cycles - 0.5 hour

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

AC-PACL(DD)	24.613 minutes
AC-PACL(DD)+TRAS	29.158 minutes

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

AC-PACL(DD)	55.75 minutes
AC-PACL(DD)+TRAS	65.75 minutes

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K - References

Citron M, Berry D, Cirrincione C, et al. Randomized trial of dose dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B trial 9741. J Clin Oncol; 2003 Apr 15. 21(8): 1431-1439.

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

PEBC Advice Documents or Guidelines

- Optimal Systemic Therapy for Early Female Breast Cancer

February 2022 Removed trastuzumab EBP forms; updated Rationale and uses section, Drug Regimen and Cycle Frequency sections

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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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