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
Neoadjuvant treatment for non-metastatic breast cancer (inoperable locally advanced, inflammatory or to downsize tumour pre-surgery) or Adjuvant therapy for node-positive and high risk node-negative breast cancer patients.
Trastuzumab may be used concurrently with paclitaxel or after completion of paclitaxel in:

- high-risk (node-positive or negative with tumour > 1cm) HER-2 positive breast cancer
- or small tumours (≤1 cm, node negative) in HER-2 positive breast cancer as part of the evidence building program

**Supplementary Public Funding**

**PACLitaxel**
New Drug Funding Program (Paclitaxel - Adjuvant Treatment for Breast Cancer)

**PACLitaxel**
New Drug Funding Program (Paclitaxel - Neoadjuvant Treatment for Non-Metastatic Breast Cancer)

**trastuzumab**
New Drug Funding Program (Trastuzumab - Adjuvant Treatment for HER2_neu-Overexpressing Primary Breast Cancer)

**trastuzumab**
Evidence Building Program (Trastuzumab (EBP) - Adjuvant Treatment for Breast Cancer)

**trastuzumab**
Evidence Building Program (Trastuzumab (EBP) - Adjuvant Treatment for Breast Cancer Supplemental)
B - Drug Regimen

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

**Alternative trastuzumab schedule:**

**trastuzumab** 4 mg /kg IV loading dose Day 1, cycle 1 only

THEN,

**trastuzumab** 2 mg /kg IV Weekly (Q7 days)

C - Cycle Frequency

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

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

Any use of the information is subject, at all times, to CCO’s Terms and Conditions.

CCO Formulary - January 2019
D - Premedication and Supportive Measures

**Antiemetic Regimen:**
- High (AC)
- Low (Paclitaxel)

**Febrile Neutropenia Risk:**
- High

Give filgrastim* 5 mcg/kg/day SC on days 3 to 10, in AC and PACL cycles.

* or alternative

Also 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 20mg PO 12 & 6 hours or 20mg IV 30 minutes before paclitaxel
  - Diphenhydramine 50mg IV 30 minutes before paclitaxel administration
  - Ranitidine 50mg IV 30 minutes before paclitaxel administration

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

**Hematologic Toxicities:** See Appendix 6 for general recommendations.

<table>
<thead>
<tr>
<th>Toxicity Type / Counts x 10^9/L</th>
<th>Toxicity Type / Counts x 10^9/L</th>
<th>Doxorubicin (% previous dose)</th>
<th>Cyclophosphamide (% previous dose)</th>
<th>Paclitaxel (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt; 1.5 Or Platelet &lt; 100</td>
<td></td>
<td>Hold *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile Neutropenia, or Grade 4 ANC ≥ 7d Or Thrombocytopenic bleeding</td>
<td>Hold * then 75%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC ≥ 1.5 And Platelet ≥ 100</td>
<td></td>
<td>100%</td>
<td>Not applicable</td>
<td>80%*</td>
</tr>
</tbody>
</table>

Grade 3/4 Neurotoxicity

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 ≥ 10^9/L, and ANC ≥ 1.5 x 10^9/L.

### Hepatic Impairment

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>AST/ALT</th>
<th>Cyclophosphamide (%)</th>
<th>Doxorubicin (%)</th>
<th>Paclitaxel (% of previous / mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 x ULN</td>
<td>and/or</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>2-4 x ULN</td>
<td>2-4 xULN</td>
<td>Caution</td>
<td>25%</td>
<td>135mg/m²</td>
</tr>
<tr>
<td>&gt;4 x ULN</td>
<td>&gt;4 x ULN</td>
<td>Caution</td>
<td>Discontinue</td>
<td>50mg/m² or OMIT</td>
</tr>
</tbody>
</table>

Any use of the information is subject, at all times, to CCO’s Terms and Conditions.
Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Cyclophosphamide</th>
<th>Doxorubicin</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&gt;30-50)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>(10-30)</td>
<td>50-75%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>(&lt;10)</td>
<td>50% or OMIT</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Very common (≥ 50%)</th>
<th>Common (25-49%) (10-24%)</th>
<th>Less common, but may be severe or life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alopecia</td>
<td>• Hypersensitivity reactions (with PACL)</td>
<td>• Edema</td>
</tr>
<tr>
<td>• Myelosuppression ± infection, bleeding (may be severe)</td>
<td>• Diarrhea</td>
<td>• ↑ LFTs (with PACL)</td>
</tr>
<tr>
<td>• Nausea and vomiting (more likely with AC)</td>
<td>• Neuropathy (may be severe; with PACL)</td>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Musculoskeletal pain (more likely with PACL)</td>
<td></td>
<td>• Abdominal pain</td>
</tr>
</tbody>
</table>

| | | | Uncommon (< 10%), |
| | | | but may be severe or life-threatening |
| | | | • Cardiotoxicity |
| | | | • Secondary leukemia/malignancies |
| | | | • Arterial/Venous Thromboembolism |
| | | | • Pneumonitis |
| | | | • SIADH |
| | | | • DIC, Hemolytic Uremic Syndrome |
| | | | • Rhabdomyolysis |
| | | | • Pancreatitis, GI obstruction, perforation |
| | | | • Radiation Recall |
| | | | • Injection Site reactions |
| | | | • Encephalopathy |
AC-PACL(DD)
AC-PACL(DD)+TRAS

- Seizures
- Vasculitis
- QTc Prolongation
- Optic neuritis
- Cystoid macular edema

G - Interactions

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

H - Drug Administration and Special Precautions

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

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

- 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/m²

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

### J - Administrative Information

**Approximate Patient Visit**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AC: 1 to 1.5 hours; Paclitaxel: 5 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-PACL(DD)</td>
<td></td>
</tr>
<tr>
<td>AC-PACL(DD)+TRAS</td>
<td>AC: 1 to 1.5 hours; Paclitaxel hours: 5; TRAS: First cycle - 1.5 hours; Subsequent cycles - 0.5 hour</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-PACL(DD)</td>
<td>24.613</td>
</tr>
<tr>
<td>AC-PACL(DD)+TRAS</td>
<td>29.158</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-PACL(DD)</td>
<td>55.75</td>
</tr>
<tr>
<td>AC-PACL(DD)+TRAS</td>
<td>65.75</td>
</tr>
</tbody>
</table>

### K - References


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

**PEBC Advice Documents or Guidelines**

- [Optimal Systemic Therapy for Early Female Breast Cancer](#)

January 2019 Updated Adverse Effects section.
**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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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