Regimen Monograph

A - Regimen Name

AC-DOCE Regimen

ADRIAMYCIN ® (DOXOrubicin)-Cyclophosphamide then DOCEtaxel

AC-DOCE+TRAS Regimen

ADRIAMYCIN ® (DOXOrubicin)-Cyclophosphamide then DOCEtaxel 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 docetaxel or after completion of docetaxel in HER-2 positive breast cancer.

Supplementary Public Funding	**trastuzumab** New Drug Funding Program (Trastuzumab (Biosimilar) - Adjuvant Treatment for Breast Cancer)

back to top

B - Drug Regimen

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

AC: (x 4 cycles)

DOXOrubicin (Round to nearest 1mg)	60 mg /m²	IV	Day 1
cyclophosphamide (Round to nearest 10mg)	600 mg /m²	IV	Day 1

THEN

Docetaxel (Taxotere®): (x 4 cycles)

DOCEtaxel (Round to nearest 5mg)	100 mg /m²	IV	Day 1

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

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

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

AC X 4 cycles then Docetaxel (Taxotere®) X 4 cycles

Trastuzumab: Refer to TRAS (Breast - Adjuvant) regimen for details.

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen:	High (AC) Low (Docetaxel)
Febrile Neutropenia Risk:	High Consider G-CSF prophylaxis for patients at high risk of febrile neutropenia. See G-CSF recommendations.

Other Supportive Care:

- With docetaxel cycles: Dexamethasone 8 mg bid po for 3 days starting 1 day prior to docetaxel (prevent anaphylaxis / fluid retention.)
- With docetaxel, consider antibiotic prophylaxis or G-CSF according to local guidelines
- Trastuzumab: Refer to Trastuzumab drug monograph for full details.

back to top

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.

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

Dosage with toxicity

Worst Toxicity Type / Counts x 10^9/L		**Worst Toxicity Type / Counts x 10^9/L**	**Doxorubicin (% previous dose)**	**Cyclophosphamide (% previous dose)**	**Docetaxel (% previous dose)**
ANC < 0.5 ≥ 7 days, or Febrile neutropenia	Or	Thrombocytopenic bleeding	Hold*, then 75% (or consider GCSF – for isolated neutropenia)		Hold*, then 75% (or consider GCSF – for isolated neutropenia)
Grade 3 Neurotoxicity	or	Grade 3 skin toxicity	Not applicable		75%*; Discontinue if recurs
Cystoid macular edema			Not applicable		Hold and investigate; refer patient promptly an ophthalmic examination. Discontinue if confirmed.
Worst Toxicity Type / Counts x 10^9/L		**Worst Toxicity Type / Counts x 10^9/L**	**Doxorubicin (% previous dose)**	**Cyclophosphamide (% previous dose)**	**Docetaxel (% previous dose)**
Other Grade 3 related organ / non-hematologic			75%* for suspect drug(s). If cardiotoxicity, follow recommendations in doxorubicin drug monograph.		
Grade 4 related organ / non-hematologic			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

	AST and/or ALT		Alk Phosp	Cyclophosphamide (% previous)	Doxorubicin (% previous)	Docetaxel (% previous)
Mild-moderate	> 1.5 -3.5 X ULN	AND	> 2.5 to 6 x ULN	100%; caution with moderate hepatic impairment	50-75%	Do not treat
Severe	> 3.5 x ULN	OR	> 6 x ULN	Caution	Discontinue	Do not treat. Discontinue* if treatment already started.

*Discontinue if Bilirubin > ULN and any AST/ALT, Alk phosp

Renal Impairment

Creatinine Clearance (mL/min)	DOXOrubicin (% previous dose)	cyclophosphamide (% previous dose)	DOCEtaxel (% previous dose)
>50	No change	100%	No change
10-50	No change	75%	No change
<10	No change	Use with extreme caution or discontinue	No change

Dosage in the Elderly

No dosage adjustment required, but caution should be exercised in elderly patients with poor performance status who are receiving docetaxel.

The risk of cardiac dysfunction and myelosuppression may be increased in elderly patients on trastuzumab. The reported trials did not determine differences in efficacy between patients > 65 years versus younger patients.

back to top

F - Adverse Effects

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

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Nausea and vomiting, diarrhea, stomatitis • Cystitis • Myelosuppression ± infection, bleeding (may be severe) • Alopecia • Hypersensitivity (may be severe) • Fluid retention (may be severe) • Neuropathy (may be severe) • Cutaneous (may be severe) • Fatigue • Musculoskeletal pain • ↑ LFTs (may be severe) • Lacrimation / lacrimal duct obstruction	• Cardiotoxicity • Secondary malignancies • Arterial thromboembolism • Venous thromboembolism • Pneumonitis • GI perforation/obstruction • SIADH • DIC, hemolytic uremic syndrome • Rhabdomyolysis • Cystoid macular edema

back to top

G - Interactions

Refer to DOXOrubicin, cyclophosphamide, DOCEtaxel (± trastuzumab) drug monograph(s) for additional details

back to top

H - Drug Administration and Special Precautions

Refer to DOXOrubicin, cyclophosphamide, DOCEtaxel (± trastuzumab) drug monograph(s) for additional details

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

back to top

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
- 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
- Clinical toxicity assessment (including stomatitis, cardiotoxicity, local toxicity, cystitis, neurologic, infection, bleeding, skin and nails, hypersensitivity, GI, respiratory, fatigue, fluid retention, ophthalmic, musculoskeletal pain, thromboembolism); at each visit

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

back to top

J - Administrative Information

Approximate Patient Visit	
AC-DOCE	AC: 1 to 1.5 hours; DOCE: 2 hours
AC-DOCE+TRAS	AC: 1 to 1.5 hours; DOCE: 2 hours; TRAS: First cycle - 1.5 hours;

Subsequent cycles - 0.5 hour

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

AC-DOCE	27.25 minutes
AC-DOCE+TRAS	32.595 minutes

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

AC-DOCE	55.417 minutes
AC-DOCE+TRAS	65.417 minutes

back to top

K - References

Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003;21(22):4165-74.

Eiermann W, Pienkowski T, Crown J, et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. J Clin Oncol 2011;29(29):3877-84.

Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365(14):1273-83.

Swain SM, Jeong JH, Geyer CE Jr, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med 2010;362(22):2053-65.

PEBC Advice Documents or Guidelines

- Optimal Systemic Therapy for Early Female Breast Cancer

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

back to top

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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back to top