Regimen Monograph

A - Regimen Name

CRBPDOCETRAS Regimen

CARBOplatin-DOCEtaxel-Trastuzumab (DCH)

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 or high risk node-negative, and HER-2 positive early 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**.

Q3 Weekly Chemotherapy:

DOCEtaxel	75 mg /m²	IV	Day 1
CARBOplatin[1]	AUC 6	IV	Day 1

[1]Adjust Carboplatin dose to AUC target (using Calvert formula) as outlined in "Other Notes" section.

PLUS

Q3 Weekly Trastuzumab Dosing

trastuzumab	8 mg /kg	IV over 90 minutes	Day 1 (Loading dose - first cycle only)
then			
trastuzumab	6 mg /kg	IV over 30 minutes*	Day 1 (starting second cycle)

*if loading dose is well-tolerated

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Docetaxel and Carboplatin: For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

Trastuzumab: To be given concurrently with docetaxel and carboplatin and continued for up to 1 year, unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)

Febrile Neutropenia Risk: High

Consider G-CSF prophylaxis for patients at high risk of febrile neutropenia. See G-CSF recommendations.

Other Supportive Care:

- Dexamethasone 8 mg bid po for 3 days starting 1 day prior to docetaxel (prevent anaphylaxis / fluid retention.)
- Trastuzumab: To prevent recurrence of infusion-associated reactions, acetaminophen and diphenhydramine may be given as pre-medication. Refer to Trastuzumab drug monograph for full details.
- Consider antibiotic prophylaxis or G-CSF according to local guidelines.

Also refer to CCO Antiemetic Recommendations.

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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.

In general, the dose of trastuzumab should be delayed if the chemotherapy cycle is delayed for scheduling convenience; if the delay is > 1 week, loading dose should be repeated.

Dosage with toxicity

Toxicity Type/ Counts x10^9/L		**Toxicity Type/ Counts x10^9/L**	**Carboplatin**[1]	**Docetaxel (% previous)** [1]
Febrile Neutropenia / Thrombocytopenic bleeding	OR	Grade 4 ANC ≥ 7 d or grade 4 platelets	↓ 1 AUC[1] or GCSF	75%[1] or GCSF
Grade 3 non-hematologic/ organ			↓ 1 AUC[1]	75%[1]; discontinue if recurs
Any occurrence of cystoid macular edema			No change	Hold and investigate; refer patient promptly to an ophthalmic examination. Discontinue if confirmed.
Grade 4 non-hematologic / organ			Discontinue	Discontinue

[1]Do not start new cycle until toxicities have recovered to ≤ grade 2, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.

Trastuzumab:

Product Monograph Recommendations

- Trastuzumab should be held with a fall in LVEF (if LVEF falls ≥10 points from baseline and/or if LVEF falls to < 50%). Repeat LVEF in 3 weeks and consider discontinuing. Discontinue if clinically significant cardiac dysfunction or cardiac failure develops.

Canadian Consensus Guidelines

- Discontinue if symptomatic.

Management of trastuzumab therapy in adjuvant breast cancer patients with asymptomatic decreases in LVEF (Mackey et al 2008):

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**	**≥ 15 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

Hypersensitivity:

Toxicity	**Trastuzumab**	**Docetaxel**
Mild hypersensitivity reaction	↓ infusion rate (and/ or hold) and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate. Consider premedication for next infusion.	
Moderate hypersensitivity reaction	Hold and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate; complete infusion at ↓ rate if possible. Use premedication for next infusion.	
Severe hypersensitivity reaction or Pulmonary Toxicity	Hold and manage symptoms aggressively with beta-agonists, antihistamines, antipyretics, and/or corticosteroids. Discontinue permanently and do not rechallenge.	

Hepatic Impairment

	AST and/or ALT		**Alk Phosp**		**Bilirubin**	**Docetaxel (% previous dose)**	**Carboplatin or Trastuzumab**
Mild-moderate	> 1.5 X ULN	AND	> 2.5 x ULN			Do not treat	No change
Severe	> 3.5 x ULN	OR	> 6 x ULN	OR	> ULN	Do not treat. Discontinue if treatment already started.	

Renal Impairment

Creatinine Clearance (mL/min)	**DOCEtaxel (% previous dose)**	**CARBOplatin (% previous dose)**	**trastuzumab (% previous dose)**
20 - 50	No adjustment appears to be required.	Use Calvert formula (Refer to "Other Notes" section)	No adjustment appears to be required.
<20		Discontinue	

Dosage in the Elderly

For docetaxel, no adjustment required, but caution should be exercised in elderly patients with poor performance status.

For carboplatin, caution should be exercised and dose reduction considered as elderly patients may have more severe myelosuppression and neuropathy.

For trastuzumab, no adjustment 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 trastuzumab, DOCEtaxel, CARBOplatin drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Headache • Fatigue • Diarrhea (may be severe) • Nausea/vomiting, stomatitis • Musculoskeletal pain • Cardiotoxicity (may be severe) • Infusion-related reaction (may be severe) • Myelosuppression ± infection, bleeding (may be severe) • Fluid retention (may be severe) • Neuropathy (may be severe) • Cutaneous effects (including nails, may be severe) • Alopecia • Lacrimation, tear duct obstruction • Nephrotoxicity (may be severe) • Electrolyte abnormalities	• Arterial thromboembolism • Venous thromboembolism • Pancreatitis • Pneumonitis • Arrhythmia • Secondary malignancies • GI obstruction, perforation • Disseminated Intravascular Coagulation • Hemolytic-uremic syndrome • Cystoid macular edema

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G - Interactions

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

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H - Drug Administration and Special Precautions

Refer to trastuzumab, DOCEtaxel, CARBOplatin 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

- 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; also as clinically indicated
- CBC; baseline and regular
- Liver and renal function tests; baseline and routine
- Electrolytes (including magnesium); baseline and regular
- Clinical toxicity assessment for neurotoxicity, ototoxicity, bleeding, infection, nausea and vomiting, pulmonary toxicity, diarrhea, infusion reactions, fluid retention, cutaneous reactions, thromboembolism, musculoskeletal pain, ophthalmic effects.

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

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J - Administrative Information

Approximate Patient Visit	First cycle: 3 to 4 hours; Subsequent cycles: 2 to 3 hours
Pharmacy Workload (average time per visit)	44.745 minutes
Nursing Workload (average time per visit)	67.500 minutes

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K - References

Carboplatin, docetaxel, trastuzumab drug monographs, Cancer Care Ontario.

Mackey JR, Clemons M, Cote, MA, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian trastuzumab working group. Current Oncology 2008; 15: 24-35.

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

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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L - Other Notes

Calvert Formula

DOSE (mg) = target AUC X (GFR + 25)

- Target AUC of 4 to 6 mg/mL·min (previously treated patients) or 6 to 8 mg/mL·min (previously untreated patients)
- AUC = product of serum concentration (mg/mL) and time (min)
- GFR (glomerular filtration rate) expressed as measured Creatinine Clearance or estimated from Serum Creatinine (by Cockcroft and Gault method or Jelliffe method)

(Calvert AH, Newell DR, Gumbrell LA, et al, Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol, 1989; 7: 1748-1756)

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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

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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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