BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Breast Cancer Using Fluorouracil, Epirubicin and Cyclophosphamide Followed by DOCEtaxel and Trastuzumab

Protocol Code	*BRAJFECDT*
Tumour Group	*Breast*
Contact Physician	*BR Systemic Therapy*

ELIGIBILITY:
Patient must have:
- Node positive (any T, N1-3) or high risk, node negative early stage breast cancer showing over-expression of HER-2
- HER-2 over-expression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- Less than or equal to 65 years of age or fit patients greater than 65 years deemed appropriate by supervising physician

Patient should have:
- ECOG 0 to 1
- Anticipated survival of greater than 5 years
- Adequate marrow, renal, and hepatic function
- No clinically significant cardiac disease
- LVEF greater than or equal to 50%*
  * If the LVEF is between 45-50%, the oncologist may decide to treat based on clinical assessment

EXCLUSIONS:
- ECOG 2 to 4
- Significant hepatic dysfunction
- Significant cardiovascular disease and/or LVEF less than 45%
- Greater than or equal to Grade 2 sensory or motor neuropathy
- Pregnancy or lactation
- Unsuitable for aggressive adjuvant chemotherapy

TESTS:
- Baseline: CBC & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase, GGT, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Baseline, if clinically indicated: LDH, MUGA scan or echocardiogram
- Before each treatment (Day 1): CBC & Diff
- Prior to **Cycle #4**: CBC & Diff, total bilirubin, alkaline phosphatase, ALT (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel)
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab and every 3 to 4 months until completion of treatment per the discretion of the treating physician. The maximum time between cardiac monitoring should be 4 months (see dose modification #5 for adjustment of trastuzumab based on changes in LVEF)
- If clinically indicated: total bilirubin, alkaline phosphatase, ALT, GGT, LDH, creatinine, MUGA scan or echocardiogram

Activated: 1 Mar 2011 Revised:1 Mar 2026 (Dose banding added, contact info, exclusions, hyperlink updated, units of measure clarified, minor formatting)

PREMEDICATIONS:

- For the 3 cycles of epirubicin, fluorouracil and cyclophosphamide - Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- For the 3 cycles of DOCEtaxel and trastuzumab:
  - Dexamethasone 8 mg PO BID for 3 days, starting one day prior to each DOCEtaxel administration. Patient must receive minimum of 3 doses pre-treatment.
  - Additional antiemetics not usually required.
  - DOCEtaxel-induced onycholysis and cutaneous toxicity of the hands may be prevented by wearing frozen gloves starting 15 minutes before DOCEtaxel infusion until 15 minutes after end of DOCEtaxel infusion; gloves should be changed after 45 minutes of wearing to ensure they remain cold during the entire DOCEtaxel infusion.

TREATMENT:

Cycles 1 to 3

Drug	Dose	BC Cancer Administration Guideline
epirubicin	100 mg/m^2 on Day 1	IV push
fluorouracil	500 mg/m^2 on Day 1	IV push
cyclophosphamide	500 mg/m^2 on Day 1	IV in 100 to 250 mL NS over 20 to 60 minutes
filgrastim (G-CSF)	5mcg/kg/day starting on Day 3, for 5 to 7 doses (adjust as needed**)	subcutaneously

**reduce filgrastim treatment duration if ANC greater than 10 x 10^9/L or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

- Repeat every 21 days for 3 cycles
- Followed by 3 consecutive cycles of DOCEtaxel and trastuzumab to start **21 days after** final cycle of epirubicin, fluorouracil and cyclophosphamide

Cycle 4

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	8 mg/kg*	IV in 250 mL NS over 90 minutes Observe for 1 hour post-infusion
DOCEtaxel	100 mg/m^2	IV in 250 to 500 mL NS over 60 minutes (use non-DEHP equipment)
filgrastim (G-CSF)	5mcg/kg/day starting on Day 3, for 5 to 7 doses (adjust as needed**)	subcutaneously

* select dose per Dose Banding Table (appendix)

**reduce filgrastim treatment duration if ANC greater than 10 x 10^9/L or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

Cycles 5 and 6

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg*	▪ IV in 250 mL NS over 60 minutes on the second dose (Cycle 5). Observe for 30 minutes post infusion ▪ IV in 250 mL NS over 30 minutes on the third dose (Cycle 6), Observe for 30 minutes post infusion
DOCEtaxel	100 mg/m^2	IV in 250 to 500 mL NS over 60 minutes (use non-DEHP equipment)
filgrastim (G-CSF)	5mcg/kg/day starting on Day 3, for 5 to 7 doses (adjust as needed**)	subcutaneously

* select dose per Dose Banding Table (appendix)
**reduce filgrastim treatment duration if ANC greater than 10 x 10^9/L or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

- Repeat every 21 days for 3 cycles.
- Followed by 14 consecutive cycles of trastuzumab to start 21 days after the final cycle of DOCEtaxel/trastuzumab for a total of 1 year of trastuzumab treatment. See BC Cancer Protocol **BRAJTR**

Radiation:

For patients with indications for radiation, the radiation treatment should be given at the usual time after the completion of the chemotherapy with the trastuzumab continued during the radiation therapy. There has been no increased toxicity reported in the clinical trials at this time, but there is no long term data; therefore, patients should be monitored. There have been no studies of concurrent trastuzumab and internal mammary node radiation, so it is unclear at this time whether there would be an enhanced risk of cardiotoxicity. If there is an anticipated need for internal mammary node radiation, it may be helpful to discuss the overall treatment program and timing with the treating radiation oncologist at the outset of chemotherapy.

DOSE MODIFICATIONS:

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" in the BC Cancer Drug Manual Appendix.

Doses are adjusted based on Day 1 counts (Tables 1 to 3) and previous cycle febrile neutropenia (Table 4). No dose reduction for nadir counts.

1. Hematological
For epirubicin, fluorouracil, cyclophosphamide and DOCEtaxel

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
Greater than or equal to 1.0	and	Greater than or equal to 100	100%
Less than 1.0	and	Greater than or equal to 100	Delay for 1 week (or longer if needed), then give 100% dose if ANC greater than 1.0 and platelets greater than or equal to 100. Give filgrastim on Days 3 to 13 for remaining cycles.
Greater than or equal to 1.0	and	Less than 100	Delay for 1 week (or longer if needed), then give 75% if ANC greater than 1.0 and platelets greater than or equal to 100
Less than 1.0	and	Less than 100	Delay for 1 week (or longer if needed), then give 75% if ANC greater than 1.0 and platelets greater than or equal to 100

Table 5. Febrile Neutropenia

Event	Management
1st episode	75% of previous cycle dose if Day 1 ANC greater than or equal to 1.0 and platelets greater than or equal to 100
2nd episode	50% of original cycle dose if Day 1 ANC greater than or equal to 1.0 and platelets greater than or equal to 100
3rd episode	Discontinue treatment

2. **Stomatitis**: For Grade 3 or 4 stomatitis (painful erythema, edema or ulcers and *cannot eat*; mucosal necrosis and/or requires enteral support; dehydration), delay until recovered then give 75% dose of Day 1 of previous cycle. Maintain dose reduction for all subsequent cycles.

3. **Hepatic Dysfunction**: Dose modification required for epirubicin if total bilirubin greater than or equal to 25 micromol/L, for fluorouracil if greater than 85 micromol/L (see Cancer Drug Manual) and for DOCEtaxel (refer to Cancer Drug Manual monograph for DOCEtaxel).

4. **Renal Dysfunction**: Dose modification may be required for cyclophosphamide if creatinine clearance less than 0.3 mL/sec, i.e., less than 18 mL/minute (see Cancer Drug Manual)

5. **Cardiac Dysfunction**

Asymptomatic Patients – Trastuzumab continuation based on serial LVEFs

Relationship of LVEF to LLN	Absolute Decrease of less than 10 points from baseline	Absolute Decrease of 10 to15 points from baseline	Absolute Decrease of greater than or equal to 16 points from baseline
Within Normal Limits	Continue	Continue	Hold*
1 to 5 points below LLN	Continue	Hold*	Hold*
Greater than or equal to 6 points below LLN	Continue*	Hold*	Hold*

- *Repeat LVEF assessment after 3 to 4 weeks, consider cardiac assessment
- If criteria for continuation are met – resume trastuzumab
- If 2 consecutive holds or a total of 3 holds occur, discontinue trastuzumab

Symptomatic Patients
- Symptomatic patients with evidence of cardiac dysfunction should have trastuzumab discontinued

For evidence of cardiac dysfunction likely related to trastuzumab and/or chemotherapy protocols, consider consulting a cardiologist, or review the following reference:
Mackey JR, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol 2008;15(1): 24-31.

6. **Treatment Interruptions – Trastuzumab**
If an interruption in treatment of greater than 6 weeks occurs (i.e. more than 6 weeks has elapsed since the last treatment was given), consider repeating the loading dose of 8 mg/kg, and then resume usual dosing.

PRECAUTIONS:

1. **Extravasation**: *Epirubicin and DOCEtaxel* cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
2. **Febrile Neutropenia:** Risk of febrile neutropenia is greater than 20% without the use of filgrastim. Mandatory filgrastim reduces the risk of febrile neutropenia. Febrile neutropenia can result in patient harm, treatment delays and hospitalization. Fever or other evidence of infection must be assessed promptly and treated aggressively.
3. **Cardiac Toxicity:** Clinical cardiac assessment is required prior to FEC if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO). **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
4. **Fluid Retention (DOCEtaxel)**: Dexamethasone premedication must be given to reduce incidence and severity of fluid retention with DOCEtaxel.
5. **Hepatic Dysfunction (DOCEtaxel)**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST or ALT) may lead to increased toxicity and usually requires a dose reduction. Baseline liver enzymes are recommended before cycle 1 and then if clinically indicated (e.g., repeat liver enzymes prior to each treatment if liver enzymes are elevated or there is severe toxicity such as neutropenia). Note: this information is intended to provide guidance but physicians must use their clinical judgment when making decisions regarding monitoring and dose adjustments.
6. **Hypersensitivity** reactions to DOCEtaxel are common but it is not necessary to routinely initiate the infusion slowly. If slow initiation of infusion is needed, start infusion at 30 mL/h x 5 minutes, then 60 mL/h x 5 minutes, then 120 mL/h x 5 minutes, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 minutes and then complete infusion at 500 mL/h). Refer to BC Cancer Hypersensitivity Guidelines.
   Alternative therapy with protocol BRAJPNT is available for moderate to severe hypersensitivity reaction that occurs despite premedications, or in those patients who cannot be managed with premedications due to a strong contraindication.
7. **Interstitial pneumonitis (DOCEtaxel)** may occur. Risk may be increased with radiation therapy.
8. **Possible drug interactions with fluorouracil and warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (e.g., for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping fluorouracil).
9. **Trastuzumab infusion-associated symptoms,** usually chills and fever, occur in 40% of patients during the first trastuzumab infusion (infrequent with subsequent infusions). Other signs and symptoms may include nausea, vomiting, pain (sometimes at tumour sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. Symptoms may be treated with acetaminophen, diphenhydrAMINE and meperidine with or without an infusion rate reduction.
   Rarely, serious infusion-related reactions have been reported (3 per 1000 patients) sometimes leading to death (4 per 10,000). Reactions include dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, and, uncommonly, allergic-like reactions. Patients experiencing dyspnea at rest due to

pulmonary metastases and other pulmonary/cardiac conditions may be at increased risk of a fatal infusion reaction and should be treated with extreme caution, if at all. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.

10. **CNS Metastases on Adjuvant Trastuzumab:** Patients with HER-2/neu over-expression have been observed to have a higher than usual risk of developing CNS metastases. The CNS is a sanctuary site, unreached by most adjuvant systemic agents. There is little or no data to guide physicians in the circumstance of a patient developing isolated CNS metastasis while on adjuvant therapy with a trastuzumab-containing regimen. Aggressive local therapy (whole brain radiation with or without surgical resection) has resulted in some durable remissions. The Breast Tumour Group supports resection of metastases and CNS radiation if feasible for patients who develop limited and isolated CNS metastases while on an adjuvant trastuzumab regimen. A metastatic survey should be done to determine the best systemic management plan. Completion of the adjuvant course of trastuzumab, or continuing beyond the adjuvant course (changing to BRAVTR regimen) due to concern for occult systemic metastases is at the discretion of the treating oncologist and dependent on the individual circumstances.
11. **A possible interaction between warfarin and trastuzumab** has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.

Contact the BR Systemic Therapy physician at your regional cancer centre or the BR Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. French Adjuvant Study 5. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol 2001;19(3):602-11
2. Roche H, Fumoleau P, Spielmann M, et al. Five year analysis of the PACS 01 trial: 6 cycles of FEC100 versus 3 cycles of FEC100 followed by 3 cycles of docetaxel for the adjuvant treatment of node positive breast cancer. Breast Can Res Treat 2004;88(suppl 1): abstract 27.
3. Gelmon K, Arnold A, Verma S, et al. Pharmacokinetics (PK) and safety of trastuzumab (Herceptin®) when administered every three weeks to women with metastatic breast cancer. [Abstract 271] Proc Am Soc Clin Oncol 2001;20(1):69a.
4. Perez A, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol 2004;22:322-329.
5. Vandenberg, T, Younus, J, and Al-Hkayyat S. Febrile neutropenia rates with adjuvant docetaxel and cyclophophamide chemotherapy in early breast cancer: discrepancy between published reports and community practice – a retrospective analysis. Curr Oncol 2010 April; 17(2):2-3.
6. Soong D, Hag R, Leung MG, et al. High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. J Clin Oncol 2009;27(26):101-2.
7. Chan A, FU WH, Shih V, et al. Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. Support Care Cancer 2011, 19: 497-504.
8. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 2009;27(8):1177-83.

Appendix. Dose Bands

TRASTUZUMAB DOSE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 58		Pharmacy prepares specific dose
58	68.49	63
68.5	76.49	71.4
76.5	84.49	79.8
84.5	94.49	88.2
94.5	104.49	100.8
104.5	117.49	109.2
117.5	127.49	117.6
127.5	144.49	130.67
144.5	162.49	147
162.5	185.49	168
185.5	208.49	189
208.5	230.49	210
230.5	251.49	231
251.5	276.49	252
276.5	323.49	294
323.5	369.49	336
369.5	415.49	378
415.5	463.49	420
463.5	550.49	504
550.5	647.49	588
647.5	740.49	672
740.5	822.49	756
822.5	928.49	840
928.5	1046.49	966
1046.5	1150.49	1050
1150.5	1258.49	1176
1258.5	1390.5	1260
More than 1390.5		Pharmacy prepares specific dose