BC Cancer Protocol Summary for Adjuvant Therapy for Breast Cancer Using Trastuzumab Following the Completion of Chemotherapy (Sequential)

Protocol Code	*BRAJTR*
Tumour Group	*Breast*
Contact Physician	*Dr. Stephen Chia*

ELIGIBILITY:

- High risk early and locally advanced breast cancer with the invasive cancer showing overexpression of HER-2
  - HER-2 over expression defined as either IHC 3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
  - High risk is defined as either node positive or node negative with tumours greater than or equal to T1b (T1a still requires CAP approval) with other features to qualify for chemotherapy with either AC-paclitaxel, AC-docetaxel, or at least four cycles of anthracycline based chemotherapy.
- ECOG 0-2
- Adequate marrow, renal, and hepatic function
- Anticipated survival of greater than 5 years
- No clinically significant cardiac disease
- LVEF greater than or equal to 50%* after the AC portion of chemotherapy
  * If LVEF at 45-50%, oncologist may decide to treat based on clinical assessment
- Being treated or treated approximately within last three months for cure with adjuvant chemotherapy
- Completed adjuvant treatment after July 1, 2004 for sequential treatment.
- Completed BRAJACTT, BRAJACTTG, BRAJDCARBT, BRLAACDT, BRAJFECDT, BRAJTDC, BRAJTRAPW, or UBRAJTTW

Note: If patients discontinue trastuzumab emtansine (KADCYLA) due to side effects, they can receive trastuzumab (BRAJTR)

EXCLUSIONS:

- Significant cardiovascular disease and/or LVEF less than 50%; if initial reading is less than 50%, physician may consider repeating for validity, or assessing LVEF by the other modality, e.g. echocardiogram instead of MUGA
- Patients who are not candidates for chemotherapy and are being treated with hormonal therapy only are not candidates for trastuzumab as there is no evidence at this time for the addition of trastuzumab to hormonal treatment in low risk disease.

TESTS:

- Baseline: CBC & diff, platelets
- MUGA scan or echocardiogram: prior to first treatment with trastuzumab and every 3-4 months during the treatment per the discretion of the treating physician. The maximum time between cardiac monitoring should be 4 month (see dose modification #1 for adjustment of trastuzumab based on changes in LVEF)
- Prior to second treatment with trastuzumab and every 12 weeks from the onset of treatment (to coincide with MUGA scan or echocardiogram): CBC & diff, platelets (optional and only if indicated)
- Weight: at baseline and every scheduled physician's visit.

If clinically indicated at anytime: cardiac function, creatinine, bilirubin, GGT, ALT, LDH, Alk Phos

PREMEDICATIONS:

- Not usually required for trastuzumab

TREATMENT:

Cycle 1 only (NEW patients ONLY – Omit for patients continuing single-agent trastuzumab following a trastuzumab-containing chemotherapy regimen)

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	8 mg/kg	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion**

Cycle 2 and subsequent cycles (For patients who have just completed a trastuzumab-containing chemotherapy regimen)

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg	▪ IV in 250 mL NS over 1 hour on the second dose. Observe for 30 minutes post infusion.** ▪ IV in 250 mL NS over 30 min on all subsequent doses if no adverse reactions. Observe for 30 min post infusion.**

** Observation period not required after 3 consecutive treatments with no reaction

New Patients: Repeat every 21 days x 17 cycles

- BRAJDCARBT – 11 single-agent trastuzumab treatments
- BRAJACTT, BRAJACTTG, BRLAACDT, BRAJTDC – 13 single-agent trastuzumab treatments
- BRAJFECDT – 14 single-agent trastuzumab treatments

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:

1. 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 -15 points from baseline	Absolute Decrease Of greater than or equal to 16 points from baseline
Within Normal Limits	Continue	Continue	Hold *
1-5 points below LLN	Continue	Hold *	Hold *
greater than or equal to 6 points below LLN	Continue *	Hold *	Hold *

- *Repeat LVEF assessment after 3-4 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.

2. Weight
Weight will be measured at each scheduled physician's visit. Dose changes based on weight will be made at this time unless the patient reports a significant weight change between physician visits.

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

PRECAUTIONS:

1. **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.
2. **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.
3. **Neutropenia (uncommon):** Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **A possible interaction with warfarin** 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.[1]

Call Dr. Stephen Chia or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment.
2. JAMA 1999;282:2299-301.
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