

BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab

Protocol Code

BRAVTR

Tumour Group

Breast

Contact Physician

Dr. Stephen Chia

ELIGIBILITY:

- Over-expression of HER-2 neu
- HER-2 over-expression defined as either IHC 3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- Metastatic breast cancer progressing after 1 prior regimen (e.g., taxane)
- Metastatic breast cancer responding to 6 cycles of trastuzumab in one of the following combinations:
 - with PACLitaxel (see protocol BRAVTRAP) or docetaxel (see protocol BRAVTRAD)
 - with PACLitaxel and CARBOplatin (see protocol BRAVTPCARB)
 - with vinorelbine (see protocol BRAVTRVIN)
 - with capecitabine (see protocol BRAVTCAP)
- Patient ineligible for, or unwilling to participate in, a clinical trial
- Life expectancy greater than 3 months
- ECOG status 0-2
- No signs or symptoms of cardiac disease. For patients with equivocal cardiac status, a MUGA scan or ECHO should be done and reveal a normal left ventricular ejection fraction.

EXCLUSIONS:

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)

TESTS:

- Baseline: CBC & diff, platelets
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Prior to second treatment with trastuzumab and every 12 weeks from the onset of treatment): CBC & diff, platelets (optional and only if indicated)
- Weight: at baseline and every scheduled physician's visit.
- If clinically indicated at any time: cardiac function, Protein level, Albumin, GGT, Bilirubin, Alk Phos, LDH, ALT, Urea, creatinine, CA15-3

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	<ul style="list-style-type: none">▪ 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.

Repeat every 21 or 28 days until disease progression.

DOSE MODIFICATIONS:

- None required. Discontinue if unacceptable toxicity occurs.

1. 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.

2. Treatment Interruptions

If an interruption in treatment of greater than 6 weeks (i.e. 2 cycles) occurs, consider repeating the loading dose of 8 mg/kg, and then:

- The next cycle should follow 21 days from the re-loading dose.
 - Continue treatment with 21-day dosing cycle
 - After 6 to 8 consecutive cycles, may switch to 28-day dosing cycles

PRECAUTIONS:

1. **Cardiac toxicity:** Trastuzumab can produce ventricular dysfunction and congestive heart failure in about 2% of patients. The majority of patients who develop cardiac dysfunction are symptomatic. Regular monitoring of asymptomatic patients is not routinely necessary but may be ordered within 4-6 months of treatment with trastuzumab. If no significant decline in cardiac function is apparent, repeated testing is not generally necessary, unless the patient's medical condition changes. Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias. Most patients who develop cardiac dysfunction respond to appropriate medical therapy and in some cases (where the benefit outweighs the risk) may continue trastuzumab under close medical supervision.

- 2. 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.

- 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. Karen Gelmon 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. *JAMA* 1999;282:2299-301.
2. Slamon D, Leyland-Jones B, Shak S, Paton V et al. Addition of Herceptin™ (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2 +/MBC) markedly increases anticancer activity: a randomized, multinational controlled phase III trial. *Proc Am Soc Clin Oncol* 1998;17:98a.
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. Leyland-Jones B, Colomer R, Trudeau ME, et al. Intensive Loading Dose of Trastuzumab Achieves Higher-Than-Steady-State Serum Concentrations and Is Well Tolerated. *J Clin Oncol* 28:960-966.