

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

Protocol Code

BRAVTRVIN

Tumour Group

Breast

Contact Physician

Dr. Caroline Lohrisch

ELIGIBILITY:

- Overexpression of HER-2 neu
- HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 per BC Cancer central laboratory
- 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)

CAUTION:

- Severe hepatic dysfunction (total bilirubin greater than 50 micromol/L)

TESTS:

- Baseline: CBC & diff, platelets, total bilirubin, [ALT](#), [Alk Phos](#), [LDH](#), [GGT](#)
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Before each treatment: CBC & diff, platelets
- If clinically indicated: total bilirubin, [creatinine](#), [ALT](#), [Alk Phos](#), [GGT](#), cardiac function

PREMEDICATIONS:

- Not usually required for trastuzumab
- Antiemetic protocol for low emetogenic chemotherapy (see protocol SCNAUSEA)
- hydrocortisone 100 mg IV prior to vinorelbine if patient experiences pain on administration

TREATMENT:

Cycle 1 only – Loading Dose

Day 1

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	8 mg/kg on day 1 only	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion*, then start vinorelbine
vinorelbine	30 mg/m ² ** on days 1 and 8	IV in 50 mL NS over 6 minutes, then flush line with 75 to 125 mL NS prior to removing/capping IV access

Cycle 2 onwards

Day 1

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg on day 1 only	<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*
vinorelbine	30 mg/m ² ** on days 1 and 8	IV in 50 mL NS over 6 minutes, then flush line with 75 to 125 mL NS prior to removing/capping IV access

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

**For frail or heavily pretreated patients, start with 25 mg/m²/day on days 1 and 8. Vinorelbine dose may be initiated or increased to 35 mg/m² at the treating physician's discretion.

Repeat every 21 days x 6-8 cycles. Responding patient may be continued on treatment at the discretion of the treating physician. If vinorelbine is discontinued for any reason other than progressive disease or trastuzumab related toxicity, can continue trastuzumab until evidence of progression (see BRAVTR). Discontinue if no response after 2 cycles or unacceptable toxicity.

DOSE MODIFICATIONS:

1. Trastuzumab:

None required. Discontinue if unacceptable toxicity occurs.

2. Hematological – Vinorelbine only

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%
0.5 to less than 1.0	or	75 to less than 100	75%
less than 0.5	or	less than 75	Delay

3. Hepatic Dysfunction – Vinorelbine

Bilirubin (micromol/L)	Dose
less than 36	100%
36 – 50	50%
greater than 50	25%

4. Neuropathy: Discontinue vinorelbine if moderate or severe. To continue single agent trastuzumab, see protocol BRAVTR.

PRECAUTIONS:

- Cardiac toxicity:** Trastuzumab can produce ventricular dysfunction and congestive heart failure in about 2-4% of patients. Regular monitoring of asymptomatic patients is not routinely necessary but may be ordered within 4-6 months of treatment with trastuzumab. If no clinically 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.
- 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:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Extravasation:** Vinorelbine causes pain and tissue necrosis if extravasated. It is recommended to flush thoroughly with 75-125 mL NS after infusing vinorelbine. Hydrocortisone 100mg IV prior to vinorelbine may be of benefit. Refer to BC Cancer Extravasation Guidelines.
5. **A possible interaction between trastuzumab and 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 weekly 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. (JAMA 1999;282:2299-2301)

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

References:

1. Burstein HJ, Kuter I, Campos SM et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001;19:2722-30.
2. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. *J Clin Oncol* 2004;22:322-329
3. Andersson, Michael et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy in metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: The HERNATA Study. *J Clin Oncol* 2011;29:264-271.