

BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using PERTuzumab, Trastuzumab, and Vinorelbine as First-Line Treatment for Advanced Breast Cancer

Protocol Code:

BRAVPTRVIN

Tumour Group:

Breast

Contact Physician:

BR Systemic Therapy

ELIGIBILITY:

Patients must have:

- HER2-positive unresectable locally recurrent or metastatic breast cancer
 - HER-2 over-expression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 or HER2 copy number greater than or equal to 6.0 at a quality assured laboratory, and
- Previously untreated in the advanced setting, or
- Relapsed after at least 6 months of completing neoadjuvant or adjuvant trastuzumab-based protocol, or
- Relapsed on or after adjuvant trastuzumab emtansine (KADCYLA), and
- Been deemed ineligible for standard first-line taxane based treatment (BRAVPTRAD or BRAVPTRAT) by their treating physician

Patients should have:

- ECOG status 0 to 1
- Adequate renal and hepatic function
- Adequate hematological (ANC greater than $1.5 \times 10^9/L$ and platelets greater than $100 \times 10^9/L$) function
- No signs or symptoms of cardiac disease. For patient with equivocal cardiac status, a MUGA scan or ECHO should be done and reveal a normal left ventricular ejection fraction.

EXCLUSIONS:

Patients must not have:

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Greater than or equal to Grade 2 sensory or motor neuropathy
- ECOG 2 to 4
- Pregnancy or lactation
- Significant hepatic dysfunction
- Neoadjuvant therapy for locally advanced breast cancer is not funded

TESTS:

- Baseline: CBC & Diff, total bilirubin, ALT, alkaline phosphatase, LDH, GGT
 - If clinically indicated: CA 15-3
- If clinically indicated: MUGA scan or echocardiogram at baseline and every 12 weeks during treatment is recommended but not mandatory
- Before each treatment for **Cycles 1 to 9** (cycles with vinorelbine and the first cycle of PERTuzumab and trastuzumab only): CBC & Diff
- For ongoing treatment with PERTuzumab and trastuzumab only: CBC & Diff (optional and only if indicated)
- If clinically indicated at any time: total bilirubin, albumin, ALT, GGT, alkaline phosphatase, LDH, urea, creatinine, CA 15-3, echocardiogram or MUGA scan, ECG

PREMEDICATIONS:

- Not usually required for trastuzumab or PERTuzumab.
- For vinorelbine, use 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 – PERTuzumab (Day 1) and trastuzumab (Day 2) loading doses:

Drug	Dose	BC Cancer Administration Guideline
PERTuzumab	840 mg loading dose on Day 1	IV in 250 mL NS over 60 minutes Observe for 60 minutes post-infusion
vinorelbine	25 mg/m ² on Days 1 and 8	IV in 25 to 50 mL NS over 6 minutes, then flush line with 75 to 125 mL NS prior to removing/capping IV access
trastuzumab	8 mg/kg* loading dose on Day 2	IV in 250 mL NS over 90 minutes Observe for 60 minutes post-infusion

* Select dose per Dose Banding Table (appendix)

Cycles 2 to 8 (all drugs may be given on the same day if Cycle 1 tolerated):

Drug	Dose	BC Cancer Administration Guideline
PERTuzumab	420 mg	<ul style="list-style-type: none"> ▪ IV in 250 mL NS over 60 minutes on the second dose, observe for 30 to 60 minutes post infusion*, ▪ IV in 250 mL NS over 30 minutes on all subsequent doses if no adverse reactions, observe for 30 to 60 minutes post infusion*
trastuzumab	6 mg/kg**	<ul style="list-style-type: none"> ▪ IV in 250 mL NS over 60 minutes on the second dose, observe for 30 minutes post infusion*, ▪ IV in 250 mL NS over 30 minutes on all subsequent doses if no adverse reactions, observe for 30 minutes post infusion*
vinorelbine	30 mg/m ^{2***} on Days 1 and 8	IV in 25 to 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

** [select dose per Dose Banding Table \(appendix\)](#)

***vinorelbine dose may be increased to 35 mg/m² at the treating physician's discretion.

Maintenance PERTuzumab and trastuzumab:

Drug	Dose	BC Cancer Administration Guideline
PERTuzumab	420 mg	IV in 250 mL NS over 30 minutes on all subsequent doses if no adverse reactions
trastuzumab	6 mg/kg*	IV in 250 mL NS over 30 minutes on all subsequent doses if no adverse reactions

* [Select dose per Dose Banding Table \(appendix\)](#)

Repeat every 21 days in responding patients. Give vinorelbine for up to 8 cycles unless disease progression or unacceptable toxicity. PERTuzumab and trastuzumab should be continued every 21 or 28 days after discontinuation of vinorelbine in responding patients without disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

1. PERTuzumab and trastuzumab:

- Dose reductions are not recommended. Doses are held or discontinued due to toxicity.
- Discontinue PERTuzumab if trastuzumab is discontinued.
- Patient may continue to receive both PERTuzumab and trastuzumab if vinorelbine is discontinued due to toxicity or after 6 to 8 cycles and without evidence of disease progression.

Missed Doses

- Re-load PERTuzumab if the time between 2 sequential infusions is greater than 6 weeks.
- Re-load trastuzumab if the time between 2 sequential infusions is greater than 6 weeks.
- If re-loading is required for either drug, the 3 drugs should be given in the same schedule as Cycle 1.
- The next cycle should follow 21 days from the re-loading dose.
 - Continue treatment with 21-day dosing cycle
 - After 8 consecutive cycles, may switch to 28-day dosing cycles

Cardiotoxicity – PERTuzumab and trastuzumab

Left Ventricular Ejection Fraction (LVEF)	PERTuzumab and trastuzumab		
	Action	LVEF at Re-assessment†	Subsequent Action
A drop in LVEF to less than 40% and asymptomatic	Hold and repeat MUGA or echocardiogram in 3 weeks	<ul style="list-style-type: none"> ▪ Recovered to greater than 45% OR ▪ 40-45% and less than 10%-points from baseline 	Restart
40-50% AND greater than 10%-points below baseline value and asymptomatic		<ul style="list-style-type: none"> ▪ Less than 40% OR ▪ 40-50% AND greater than 10%-points below baseline value and asymptomatic ▪ Symptomatic 	Discontinue
Symptomatic	Consider discontinuing	n/a	n/a

† if after repeat assessment within approximately 3 weeks, the LVEF has not improved, or declined further, discontinuation of PERTuzumab and trastuzumab should be strongly considered.

2. Vinorelbine:

2a. Hematological

ANC (x10 ⁹ /L)		Platelets (x10 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

2b. Hepatic dysfunction

Total bilirubin	Dose
Less than 36	100%
36 – 50	50%
Greater than 50	25%

2c. Neuropathy: Discontinue vinorelbine if moderate or severe. May continue PERTuzumab and trastuzumab maintenance therapy.

PRECAUTIONS:

- 1. Cardiac toxicity:** Decreases in LVEF have been reported with drugs that block HER2 activity, including PERTuzumab. However, PERTuzumab does not seem to further increase the incidence of symptomatic congestive heart failure or decreased LVEF when used in combination with trastuzumab. Trastuzumab can produce declines in ventricular dysfunction and congestive heart failure (CHF). Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias/events. Most patients who develop congestive heart failure respond to appropriate medical therapy and in some cases (where the benefit outweighs the risk) may continue treatment under close medical supervision.
- 2. PERTuzumab or 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 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 to 125 mL NS after infusing vinorelbine. Hydrocortisone 100mg IV prior to vinorelbine may be of benefit. Refer to BC Cancer Extravasation Guidelines.
5. **Hepatic Dysfunction:** Vinorelbine undergoes hepatic metabolism. Dose adjustments may be required.
6. **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 to 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;282:2299-301).

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. Perez EA, López-Vega JM, Petit T, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res.* 2016;18(1):126.
2. Andersson M, López-Vega JM, Petit T, et al. Efficacy and safety of pertuzumab and trastuzumab administered in a single infusion bag, followed by vinorelbine: VELVET Cohort 2 final results. *Oncologist.* 2017;22(10):1160-1168.

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