BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer Using PERTuzumab, Trastuzumab (HERCEPTIN), and DOCEtaxel as First-Line Treatment for Advanced Breast Cancer

Protocol Code: BRAVPTRAD
Tumour Group: Breast
Contact Physician: Dr. Stephen Chia

ELIGIBILITY:
- First-line treatment of patients with HER2-positive unresectable locally recurrent or metastatic breast cancer (patients may have received trastuzumab in the neoadjuvant or adjuvant setting, but must be relapse free for 6 months or greater)
- Over-expression of HER-2 neu
- HER-2 over-expression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 at a quality assured laboratory
- Life expectancy greater than 3 months
- ECOG status 0-1
- Adequate renal and hepatic function
- Adequate hematological (ANC greater than 1.5 x 10^9/L and platelets greater than 100 x 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:
- 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 2-4
- Pregnancy or lactation
- Significant hepatic dysfunction
- Neoadjuvant therapy for locally advanced breast cancer is not funded

TESTS:
- Baseline: CBC & diff, platelets, total bilirubin, liver enzymes
- 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 docetaxel and the first cycle of PERTuzumab and trastuzumab only): CBC & diff, platelets
- For ongoing treatment with PERTuzumab and trastuzumab only: CBC & diff, platelets (optional and only if indicated)
- Prior to Cycle 4: total bilirubin, liver enzymes
- If clinically indicated at any time: total bilirubin, liver enzymes, echocardiogram or MUGA scan
PREMEDICATIONS:

- Not usually required for trastuzumab or PERTuzumab
- For DOCEtaxel:
  - 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:

Cycle 1 – PERTuzumab (day 1) and trastuzumab (day 2) loading doses:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERTuzumab</td>
<td>840 mg loading dose Day 1</td>
<td>IV in NS 250 mL over 1 hour Observe for 1 hour post-infusion</td>
</tr>
<tr>
<td>trastuzumab (HERCEPTIN)</td>
<td>8 mg/kg loading dose Day 2</td>
<td>IV in NS 250 mL over 1 hour 30 min Observe for 1 hour post-infusion.</td>
</tr>
<tr>
<td>DOCEtaxel*</td>
<td>75 mg/m² Day 2</td>
<td>IV in NS 250 to 500 mL* over 1 hour (use non-DEHP equipment)</td>
</tr>
</tbody>
</table>

*use 250 mL for doses 74 to 185 mg, use 500 mL for doses greater than 185 mg
Cycles 2 to 8 (all drugs may be given on the same day if cycle 1 tolerated):

<table>
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</table>
| PERTuzumab                  | 420 mg | ▪ IV in NS 250 mL over 1 hour on the second dose, observe for 30 minutes to 1 hour post infusion**,  
|                             |      | ▪ IV in NS 250 ml over 30 minutes on all subsequent doses if no adverse reactions, observe for 30 minutes to 1 hour post infusion**  
|                             |      | **observation period not required after 3 consecutive treatments with no reaction |
| trastuzumab (HERCEPTIN)     | 6 mg/kg | ▪ IV in NS 250 mL over 1 hour on the second dose, observe for 30 minutes post infusion**,  
|                             |      | ▪ IV in NS 250 ml over 30 minutes 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 |
| DOCEtaxel (6 to 8 cycles only) | 75 mg/m²† | IV in NS 250 to 500 mL* over 1 hour (use non-DEHP equipment) |

* use 250 mL for doses 74 to 185 mg, use 500 mL for doses greater than 185 mg

† may consider dose escalation to 100 mg/m² if patient tolerates a least one cycle of 75 mg/m² without any of the following events: febrile neutropenia, grade 4 neutropenia for greater than 5 days, any ANC less than 0.1 x 10⁹/L for greater than 1 day, or other non-hematological toxicities greater or equal to 3.

Maintenance PERTuzumab and trastuzumab (HERCEPTIN®):

<table>
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<tr>
<th>Drug</th>
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</tr>
</thead>
<tbody>
<tr>
<td>PERTuzumab</td>
<td>420 mg</td>
<td>IV in NS 250 ml over 30 minutes on all subsequent doses if no adverse reactions</td>
</tr>
<tr>
<td>trastuzumab (HERCEPTIN)</td>
<td>6 mg/kg</td>
<td>IV in NS 250 ml over 30 minutes on all subsequent doses if no adverse reactions</td>
</tr>
</tbody>
</table>

Repeat every 21 days in responding patients. Give DOCEtaxel for up to 6 to 8 cycles unless disease progression or unacceptable toxicity. PERTuzumab and trastuzumab should be continued every 21 days after discontinuation of DOCEtaxel 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 docetaxel is discontinued due to toxicity or after 6-8 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 (e.g. PERTuzumab day 1, trastuzumab and docetaxel day 2).
- The next cycle should follow 3 weeks from the re-loading dose.

**Cardiotoxicity**

<table>
<thead>
<tr>
<th>Left Ventricular Ejection Fraction</th>
<th>PERTuzumab and Trastuzumab (HERCEPTIN®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>LVEF at Re-assessment†</td>
</tr>
<tr>
<td>a drop in LVEF to less than 40% and asymptomatic</td>
<td>Hold and repeat MUGA or echocardiogram in 3 weeks</td>
</tr>
<tr>
<td>40-50% AND greater than 10%-points below baseline value and asymptomatic</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Consider discontinuing</td>
</tr>
</tbody>
</table>

† 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. DOCEtaxel:
#### 2a. Hematological

<table>
<thead>
<tr>
<th>ANC (x $10^9$/L)</th>
<th>Platelets (x $10^9$/L)</th>
<th>Dose</th>
<th>filgrastim (G-CSF) option</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.5 and greater than 100</td>
<td>100%</td>
<td>give 100% dose with G-CSF 300 mcg sc daily on days 4 to 11 (adjust as needed)</td>
<td></td>
</tr>
<tr>
<td>1 to 1.49 and 70 to 100</td>
<td>75%†</td>
<td>delay until ANC greater (\geq) 1.5 and platelets greater than 100 and give 75% dose delay until ANC greater (\geq) 1.5 and platelets greater than 100 and give 75% dose</td>
<td></td>
</tr>
<tr>
<td>less than 1 or less than 70</td>
<td>75%†</td>
<td>give 75% dose or filgrastim option</td>
<td></td>
</tr>
</tbody>
</table>

Febrile neutropenia or grade 4 neutropenia lasting greater than or equal to 7 days in previous cycle:

- give 75% dose or filgrastim option

† Dose may be re-escalated to 100% at next cycle if ANC \(\geq\) 1.5 and platelets greater than 100 at the discretion of the treating physician.

### 2b. Hepatic Dysfunction

<table>
<thead>
<tr>
<th>Alkaline Phosphatase</th>
<th>AST +/- or ALT</th>
<th>Bilirubin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 2.5 x ULN and less than or equal to 1.5 x ULN</td>
<td>--</td>
<td>--</td>
<td>100%</td>
</tr>
<tr>
<td>2.5 to 6 x ULN and 1.6 to 3.5 x ULN</td>
<td>--</td>
<td>--</td>
<td>75%</td>
</tr>
<tr>
<td>greater than 6 x ULN or greater than 3.5 ULN</td>
<td>greater than 3.5 ULN or greater than ULN</td>
<td>discuss with contact physician</td>
<td></td>
</tr>
</tbody>
</table>

ULN = upper limit of normal
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 and docetaxel. 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. **DOCEtaxel Hypersensitivity:** Reactions 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 BCCA Hypersensitivity Guidelines

4. **Fluid retention:** Dexamethasone premedication must be given to reduce incidence and severity of fluid retention.

5. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.

6. **Extravasation:** DOCEtaxel causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.

7. **Hepatic Dysfunction:** DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction. Baseline liver enzymes are recommended before cycle 1 and then if clinically indicated (eg, repeat liver enzymes prior to each treatment if liver enzymes are elevated, liver metastases are present or there is severe toxicity such as neutropenia). If liver enzymes are normal and there is no evidence of liver metastases or severe toxicity, check liver enzymes after 3 cycles (ie, at cycle 4). Note: this information is intended to provide guidance but physicians must use their clinical judgment when making decisions regarding monitoring and dose adjustments.
8. 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;282:2299-301)

Call Dr. Stephen Chia or tumour group delegate at 604-877-600 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 01 Nov 2013
Date last revised: 1 Aug 2016 (Class II registration deleted, TALLman lettering formatted)

References: