

DRUG NAME: Trastuzumab

SYNONYM(S): anti-c-erbB-2; anti-ERB-2; MOAB HER2; rhuMAb HER2¹

COMMON TRADE NAME(S): HERCEPTIN®; HERZUMA® (biosimilar), TRAZIMERA® (biosimilar), OGIVRI® (biosimilar)

CLASSIFICATION: Monoclonal antibody

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Trastuzumab is a human monoclonal IgG antibody which selectively targets HER2, a human epidermal growth factor receptor (EGFR). Trastuzumab inhibits the growth of tumour cells that overexpress HER2 on the surface of breast, gastric, ovarian, lung, and prostate cancer cells.^{2,3} Mechanisms involved include: decreasing VEGF production, activating antibody-dependent cell-mediated cytotoxicity, G0/G1 cell cycle cytotoxicity, and inhibiting intracellular signaling pathways.^{2,4,5}

PHARMACOKINETICS:

Interpatient variability	interpatient variability noted in clearance and volume of distribution ^{2,6}	
Distribution	steady state, AUC, C _{max} , C _{min} are lower in metastatic gastric cancer than metastatic breast cancer ² ; steady state trough levels are similar between weekly and 3-weekly regimens ^{2,7,8}	
	cross blood brain barrier?	unlikely, due to large molecule size ^{1,9,10}
	volume of distribution	3-4L
	plasma protein binding	no information found
Metabolism	no information found	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	via the reticuloendothelial system ¹¹	
	urine	no information found
	feces	no information found
	terminal half life	12-29 days; shorter half life in metastatic gastric cancer due to increased clearance
	clearance	0.225-0.378 L/day; increased with more metastatic sites ^{2,6}
Elderly	no differences reported	

Adapted from standard reference² unless specified otherwise.

USES:

Primary uses:

- *Breast cancer
- *Gastric cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to trastuzumab or Chinese hamster ovary cell proteins²

Caution:

- in patients with pre-existing cardiac dysfunction or a left ventricular ejection fraction (LVEF) of 55% or less^{2,12}
- in patients with pre-existing pulmonary disease or extensive pulmonary tumour involvement¹; patients who experience dyspnea at rest due to comorbidities or advanced malignancy may be at increased risk of a fatal infusion reaction.²

Special populations:

- patients aged 65 years and older may be at greater risk for cardiac dysfunction and hematologic toxicities (leukopenia and thrombocytopenia)²
- patients who received prior adjuvant therapy with anthracyclines for treatment of early breast cancer are at greater risk of developing cardiotoxicity¹

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Trastuzumab is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.²

Fertility: Formal fertility studies have not been conducted in women. No evidence of impaired fertility was reported in animal studies.²

Pregnancy: FDA Pregnancy Category D. There is evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Impaired fetal renal growth and function, intrauterine growth retardation, and skeletal abnormalities associated with oligohydramnios during the second and third trimesters have been reported.² Women of childbearing potential are advised to use effective contraception during treatment and for at least 7 months post treatment.¹³

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, trastuzumab was detected in the milk of lactating monkeys, although no adverse effects on growth or development were seen.²

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.¹⁴⁻¹⁶

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
blood and lymphatic system/ febrile neutropenia	anemia (4%) ¹
	leukopenia (3%) ¹
cardiac	arrhythmia (3%) ¹
	<i>congestive heart failure</i> (2%; severe <1%) ^{2,17} ; see paragraph following Side Effect table
	palpitations (3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	tachycardia (1%)
gastrointestinal	<i>emetogenic potential: low¹⁸</i>
	abdominal pain (2%)
	constipation (2%)
	diarrhea (7%)
	dyspepsia (2%)
	gastritis (1%)
	nausea (6-14%) ^{2,19}
	stomatitis (2%)
	vomiting (4-28%)
general disorders and administration site conditions	<i>extravasation hazard: none²⁰</i>
	asthenia (5%)
	chills (5%)
	fatigue (8%)
	fever (6%)
	influenza-like illness (2%)
	infusion-related reaction (21-40%, severe 1%) ¹ ; see paragraph following Side Effects table
	non-cardiac chest pain (3%)
	peripheral edema (5%)
immune system	allergic reaction (3%)
infections and infestations	herpes zoster (1%)
	influenza (4%)
	nasopharyngitis (8%)
	pharyngitis (1%)
	rhinitis (2%)
	sinusitis (2%)
	upper respiratory tract infection (3%)
	urinary tract infection (2-5%) ^{1,2}
investigations	alkaline phosphatase, elevated ²¹
	ALT, elevated ²¹
	AST, elevated ²¹
	bilirubin, elevated (1%)
	ejection fraction, decreased (4-10%) ^{2,17} ; see paragraph following Side Effect table
	weight gain (2%)
musculoskeletal and	arthralgia (8%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
connective tissue	back pain (5%)
	bone pain (3%)
	chest wall pain (2%)
	muscle spasms (3%)
	myalgia (4%)
	pain in extremity (4%)
	shoulder pain (2%)
nervous system	dizziness (4%)
	headache (10%)
	paresthesia (2%)
	vertigo (2%)
psychiatric	anxiety (2%)
	depression (3%)
	insomnia (4%)
renal and urinary	cystitis (1%)
reproductive system and breast disorders	breast pain (1%)
respiratory, thoracic and mediastinal	cough (5%)
	dyspnea (3%)
	epistaxis (1%)
	pharyngolaryngeal pain (2%)
	rhinitis (2%)
skin and subcutaneous tissue	erythema (1%)
	nail disorder (3%)
	pruritus (2%)
	rash (4%)
vascular	hot flashes (6%)
	hypertension (4%)
	lymphedema (3%)

Adapted from standard reference² unless specified otherwise.

Cardiotoxicity has been reported with trastuzumab. Signs and symptoms include: dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S₃ gallop, congestive heart failure (CHF), or a reduced ejection fraction of 10% or greater.^{2,11} Cardiac dysfunction from trastuzumab is not dose-related and is reported to be highly reversible so patients have relatively good prognosis following CHF or LVEF dysfunction.^{12,17,22,23} LVEF usually returns toward baseline during the 1.5 months post-trastuzumab treatment^{2,11,22}; however, some cases have resulted in disabling heart failure, thrombosis and stroke, and/or death.^{2,11}

Risk factors for trastuzumab-related cardiotoxicity include:^{11,12,24-27}

- older age (>65 years)
- prior or concurrent use of antihypertensive medications
- higher cumulative dose of anthracycline prior to trastuzumab
- a lower left ventricular ejection fraction (LVEF) at baseline
- a declining LVEF (<55%)
- a low LVEF prior to or following paclitaxel treatment
- a higher body mass index (>25) at screening

An increase in cardiac events is observed when trastuzumab is administered after anthracycline-containing chemotherapy compared to non-anthracycline-containing chemotherapy. The incidence is more marked when trastuzumab is administered concurrently, rather than sequentially, with a taxane.²⁷ There is some uncertainty whether smoking, diabetes, hypothyroidism, or hyperlipidemia is associated with trastuzumab-related cardiotoxicity.^{12,24} Prior or concurrent radiation does not increase cardiac events, but may increase the incidence of leukopenia.^{2,28,29} There is inadequate long term data, however, to correlate cardiac dysfunction from trastuzumab with concurrent or prior radiation.^{2,28} Trastuzumab interrupts the HER2 signalling pathway in the heart which maintains normal growth, repair, and survival of cardiac cells. This results in changes to cardiac contractility, but does not cause myocardial cell death.^{12,17,22} Suggested management for trastuzumab-related cardiotoxicity includes withholding trastuzumab for approximately 3 weeks if LVEF falls 10-15 ejection points below baseline and/or below 50%.^{2,12} Trastuzumab can be resumed once LVEF improves. If the LVEF does not improve within approximately 3 weeks, consider discontinuing trastuzumab.² Trastuzumab may be considered in patients with a LVEF less than 50% if their risk of disease recurrence is very high.¹² The LVEF should be assessed prior to starting trastuzumab, repeated every 3 months during treatment, and then, every 6 months following completion of treatment until 24 months from the last dose of trastuzumab. For early breast cancer patients who received anthracycline-based chemotherapy, yearly monitoring of LVEF up to 5 years or longer from the last dose of trastuzumab is suggested.²⁷ Refer to protocol by which patient is being treated.

Infusion-related reactions range from mild reactions of chills and/or fever (occurring in 40% of patients with first infusion) to mild-moderate reactions of nausea, vomiting, pain, rigors, headache, cough, dizziness, dyspnea, rash, and asthenia. Severe reactions include hypotension, hypertension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress. Pre-existing pulmonary disease or co-morbidities may increase risk of pulmonary toxicities or a fatal reaction. Clinical course is variable; initial improvement may be followed by clinical deterioration and death. Management of infusion-related reactions includes decreasing the rate for mild or moderate reactions and interrupting the infusion in patients experiencing dyspnea or hypotension. Consider discontinuing treatment for severe reactions such as anaphylaxis, angioedema, pneumonitis, or respiratory distress. Patients who react to the initial trastuzumab infusion may receive further treatment after complete resolution of symptoms. Infusion duration may be increased at the physician's discretion. Symptoms are managed with diphenhydramine, acetaminophen, meperidine, epinephrine, corticosteroids, oxygen, bronchodilators, or IV fluids. Patients experiencing infusion-related symptoms should not drive or use machines until symptoms resolve completely.²

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anthracycline chemotherapy ^{2,10,11,27,30}	increase in trastuzumab-induced cardiac dysfunction	negative inotropic effect on the heart	avoid use of anthracyclines concurrently with trastuzumab
paclitaxel ^{2,10,11,30}	1.5 fold increase in trastuzumab serum levels	mechanism unclear; animal studies report a 2 fold decrease in trastuzumab clearance	monitor for signs of cardiac dysfunction

SUPPLY AND STORAGE:

Biosimilar formulations of trastuzumab are available.

Injection:

Hoffmann-La Roche Limited supplies trastuzumab (HERCEPTIN®) as 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution. Refrigerate.²

Celltrion Healthcare Co. Ltd. (distributed by Teva Canada Limited) supplies trastuzumab (HERZUMA®) as 150 mg and 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution of 440 mg vials. Refrigerate.³¹

BGP Pharma ULC supplies trastuzumab (OGIVRI®) as 150 mg and 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution of 440 mg vials. Refrigerate.³²

Pfizer Canada ULC supplies trastuzumab (TRAZIMERA®) as 150 mg and 440 mg vials of preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution of 440 mg vials. Refrigerate.³³

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

Additional information:

- Benzyl alcohol should not be administered intrathecally due to the risk of anaphylaxis and increased potential for neurotoxicity.^{34,35} For intrathecal administration of trastuzumab or in patients with a known hypersensitivity to benzyl alcohol:
 - reconstitute vial with sterile water for injection instead of the supplied preservative-containing diluent^{2,35,36}
 - use immediately; discard unused portion^{2,37}
- Trastuzumab should not be further diluted or administered with dextrose (5%) solution as it may cause aggregation of the protein.²

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in **bold, italics**

Subcutaneous	has been given ³⁸
Intramuscular	no information found
Direct intravenous	do not use ²

BC Cancer administration guideline noted in ***bold, italics***

<i>Intermittent infusion</i>	<i>over 30-90 minutes</i> ^{2,25,39-58} <i>3-weekly dosing:</i> <ul style="list-style-type: none"> • <i>loading dose over 90 minutes;</i> • <i>1st maintenance dose over 60 minutes;</i> • <i>2nd and further maintenance doses over 30 minutes if no adverse reactions</i> <i>Weekly dosing:</i> <ul style="list-style-type: none"> • <i>loading dose over 60 minutes;</i> • <i>maintenance doses over 30 minutes if no adverse reactions</i>
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	has been used ^{34-37,59-61}
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: <i>weekly</i> ^{45,62-66}	<i>Loading dose: 4 mg/kg IV</i> for one dose on day 1 of <i>first cycle</i> <i>Maintenance dose: 2 mg/kg IV</i> for one dose on day 1 of <i>each subsequent cycle</i>
	<i>3 weeks</i> ^{42-44,46-58,67-69}	<i>Loading dose: 8 mg/kg IV</i> for one dose on day 1 of <i>first cycle</i> <i>Maintenance dose: 6 mg/kg IV</i> for one dose on day 1 of <i>each subsequent cycle</i>
	3 weeks ⁷⁰	Loading dose: 6 mg/kg IV for one dose on days 1, 8, and 15 of first cycle Maintenance dose: 6 mg/kg IV for one dose on day 1 only of each subsequent cycle

11. AHFS Drug Information® (database on the Internet). Trastuzumab. Lexi-Comp Inc., 15 March 2012. Available at: <http://online.lexi.com>. Accessed 4 September 2012.
12. Mackey JR, Clemons M, Cote MA, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the canadian trastuzumab working group. *Curr Oncol* 2008;15(1):24-35.
13. Hoffman-La Roche Limited. HERCEPTIN® product monograph. Mississauga, Ontario; 15 July 2014.
14. Vanessa Bernstein MD. BC Cancer Agency Breast Tumour Group. Personal communication. 13 November 2012.
15. Kimberly Kuik. Pharmacist, BC Cancer Agency Breast Tumour Group. Personal communication. 23 November 2012.
16. Bal Johal MD. BC Cancer Agency Gastrointestinal Tumour Group. Personal communication. 18 October 2012.
17. Procter M, Suter TM, de Azambuja E, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin adjuvant (HERA) trial. *J Clin Oncol* 2010;28(21):3422-3428.
18. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
19. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of her2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20(3):719-726.
20. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 February 2012.
21. Srinivasan S, Parsa V, Liu CY, et al. Trastuzumab-induced hepatotoxicity. *Ann Pharmacother* 2008;42:1497-1501.
22. Ewer MS, Vooletich MT, Durand J, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005;23(31):7820-7826.
23. Telli ML, Hunt SA, Carlson RW, et al. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol* 2007;25(23):3525-3533.
24. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the Herceptin adjuvant trial. *J Clin Oncol* 2007;25(25):3859-3865.
25. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol* 2011;29(25):3366-3373.
26. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008;26(8):1231-1238.
27. Hoffman-La Roche Limited. HERCEPTIN® product monograph. Mississauga, Ontario; 16 November 2012.
28. Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III trial N9831. *J Clin Oncol* 2009;27(16):2638-2644.
29. Tsoutsou PG, Belkacemi Y, Gligorov J, et al. Optimal sequence of implied modalities in the adjuvant setting of breast cancer treatment: an update on issues to consider. *Oncologist* 2010;15:1169-1178.
30. Facts and Comparisons® Drug Interactions (database on the Internet). Trastuzumab. Wolters Kluwer Health Inc. Facts and Comparisons® eAnswers, updated monthly. Available at: <http://online.factsandcomparisons.com>. Accessed 12 September 2012.
31. Celltrion Healthcare Co Ltd (distributed by Teva Canada Limited). HERZUMA® product monograph. Toronto, Ontario; 20 October 2020.
32. BGP Pharmacy ULC. OGIVRI® product monograph. Etobicoke, Ontario; 3 May 2019.
33. Pfizer Canada ULC. TRAZIMERA® product monograph. Kirkland, Quebec; 15 August 2019.
34. Ferrario C, Davidson A, Bouganim N, et al. Intrathecal trastuzumab and thiotepa for leptomeningeal spread of breast cancer. *Ann Oncol* Apr 2009;20(4):792-795.
35. Siderov J. Care with intrathecal trastuzumab. *Lancet Oncol* Nov 2006;7(11):888.
36. Perissinotti AJ, Reeves DJ. Role of intrathecal rituximab and trastuzumab in the management of leptomeningeal carcinomatosis. *Ann Pharmacother* October 01, 2010;44(10):1633-1640.
37. Martens J, Venuturumilli P, Corbets L, et al. Rapid clinical and radiographic improvement after intrathecal trastuzumab and methotrexate in a patient with HER-2 positive leptomeningeal metastases. *Acta Oncol* 2013;52(1):175-178.
38. Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. *Lancet Oncol* 2012;13:869-878.

39. Lee R, Incekol D, Ng P. Rapid 30 minute infusion of trastuzumab 6 mg/kg every 3 weeks: cost effective and safe. *J Onc Pharm Pract* 2006;12(1):22 (abstract 13).
40. Moloney M, Kirsa S, Francis P, et al. Rapid infusion of trastuzumab 6mg/kg is safe and improves efficiency (Abstract). *JOPP* June 1, 2008;14(2):72.
41. Wendy Li. Drug Information Pharmacy Resident, Hoffman-La Roche Limited. Personal communication. 24 September 2012.
42. BC Cancer Agency Breast Tumour Group. (BRAJACTT) BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer using Doxorubicin and Cyclophosphamide followed by Paclitaxel and Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 September 2012.
43. BC Cancer Agency Breast Tumour Group. (BRAJACTTG) BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Dose Dense Therapy: Doxorubicin and Cyclophosphamide Followed by Paclitaxel and Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 June 2011.
44. BC Cancer Agency Breast Tumour Group. (BRAJDCARBT) BCCA Protocol Summary for Breast Cancer Using Docetaxel, Carboplatin, and Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 September 2012.
45. BC Cancer Agency Breast Tumour Group. (BRAJDTFEC) BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Docetaxel and Trastuzumab, and Fluorouracil, Epirubicin and Cyclophosphamide. Vancouver, British Columbia: BC Cancer Agency; 1 August 2012.
46. BC Cancer Agency Breast Tumour Group. (BRAJFECDT) BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Fluorouracil, Epirubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 September 2012.
47. BC Cancer Agency Breast Tumour Group. (BRAJTDC) BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Trastuzumab, Docetaxel and Cyclophosphamide. Vancouver, British Columbia: BC Cancer Agency; 1 September 2012.
48. BC Cancer Agency Breast Tumour Group. (BRAJTR) BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Trastuzumab (HERCEPTIN®) Following the Completion of Chemotherapy (Sequential). Vancouver, British Columbia: BC Cancer Agency; 1 September 2012.
49. BC Cancer Agency Breast Tumour Group. (BRLAACDT) BCCA Protocol Summary for Treatment of Locally Advanced Breast Cancer using Doxorubicin and Cyclophosphamide followed by Docetaxel (TAXOTERE®) and Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 April 2012.
50. BC Cancer Agency Breast Tumour Group. (BRAVTR) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 September 2012.
51. BC Cancer Agency Breast Tumour Group. (BRAVTRAD) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN®) and Docetaxel as First-Line Treatment for Advanced Breast Cancer. Vancouver, British Columbia: BC Cancer Agency; 1 June 2011.
52. BC Cancer Agency Breast Tumour Group. (BRAVTRAP) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN®) and Paclitaxel as First-Line Treatment for Advanced Breast Cancer. Vancouver, British Columbia: BC Cancer Agency; 1 June 2011.
53. BC Cancer Agency Breast Tumour Group. (BRAVTRVIN) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab and Vinorelbine. Vancouver, British Columbia: BC Cancer Agency; 1 December 2011.
54. BC Cancer Agency Breast Tumour Group. (BRAVTPCARB) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN®), Paclitaxel and Carboplatin as First-Line Treatment for Advanced Breast Cancer. Vancouver, British Columbia: BC Cancer Agency; 1 September 2012.
55. BC Cancer Agency Breast Tumour Group. (UBRAVTCAP) BCCA Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab and Capecitabine. Vancouver, British Columbia: BC Cancer Agency; 1 July 2011.
56. BC Cancer Agency Gastrointestinal Tumour Group. (GIGAVTR) BCCA Protocol Summary for Continuation of Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 February 2010.
57. BC Cancer Agency Gastrointestinal Tumour Group. (UGIGAVCCT) BCCA Protocol Summary for Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using Cisplatin, Capecitabine and Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 June 2011.
58. BC Cancer Agency Gastrointestinal Tumour Group. (UGIGAVCFT) BCCA Protocol Summary for Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using Cisplatin, Infusional Fluorouracil and Trastuzumab. Vancouver, British Columbia: BC Cancer Agency; 1 June 2011.

59. Platini C, Long J, Walter S. Meningeal carcinomatosis from breast cancer treated with intrathecal trastuzumab. *The Lancet Oncology* 2006;7(9):778-780.
60. Stemmler HJ, Schmitt M, Harbeck N, et al. Application of intrathecal trastuzumab (Herceptin™) for treatment of meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer. *Oncol Rep* 2006;15:1373-1377.
61. Stemmler HJ, Mengele K, Schmitt M, et al. Intrathecal trastuzumab (Herceptin) and methotrexate for meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer: a case report. *Anticancer Drugs Sep* 2008;19(8):832-836.
62. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *New England Journal of Medicine* 2001;344(11):783-92.
63. Pierga J, Delaloue S, Espie M, et al. A multicenter randomized phase II study of sequential epirubicin/cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. *Br Cancer Res Treat* 2010;122:429-437.
64. Inoue K, Nakagami K, Mizutani M, et al. Randomized phase III trial of trastuzumab monotherapy followed by trastuzumab plus docetaxel versus trastuzumab plus docetaxel as first-line therapy in patients with HER2-positive metastatic breast cancer: the J017360 Trial Group. *Breast Cancer Res Treat* 2010;119:127-136.
65. French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 Randomized Trial. *J Clin Oncol* 2001;19(3):602-611.
66. Joensuu H, Kellokumpu-Lehtinen P, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006;354:809-820.
67. Dowsett M, Procter M, McCaskill-Stevens W, et al. Disease-free survival according to degree of HER2 amplification for patients treated with adjuvant chemotherapy with or without 1 year of trastuzumab: the HERA trial. *J Clin Oncol* 2009;27(18):2962-2969.
68. Bang Y, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-697.
69. DeVita F, Giuliani F, Silvestris N, et al. Human epidermal growth factor receptor 2 (HER2) in gastric cancer: a new therapeutic target. *Cancer Treat Rev* 2010;36(S3):S11-S15.
70. 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* 2010;28(6):960-966.
71. Baselga J, Tripathy D, Mendelsohn J, et al. Phase II study of weekly intravenous trastuzumab (HERCEPTIN®) in patients with HER2/neu-overexpressing metastatic breast cancer. *Seminars in Oncology* 1999;26(4 Suppl 12):78-83.
72. Tokuda Y, Watanabe T, Omuro Y, et al. Dose escalation and pharmacokinetic study of a humanized anti-her2 monoclonal antibody in patients with her2/neu-overexpressing metastatic breast cancer. *Br J Cancer* 1999;81(8):1419-1425.
73. Carter P, Presta L, Gorman CM, et al. Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc Natl Acad Sci USA* May 15, 1992;89(10):4285-4289.
74. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *Journal of Clinical Oncology* 1999;17(9):2639-48.
75. Bailie GR, Mason NA. Rituximab. 2012 Dialysis of Drugs. Saline, Michigan, USA: Renal Pharmacy Consultants, LLC; 2012. p. 47.