Regimen Monograph

A - Regimen Name

CAPE+TRAS Regimen

Capecitabine-Trastuzumab

Disease Site Breast

Intent Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses For treatment of breast cancer in patients who progressed after prior chemotherapy and have had prior trastuzumab in the metastatic setting (patients may not have had progression on lapatinib). See NDFP eligibility form for additional funding criteria.

Supplementary Public Funding

capecitabine
ODB - General Benefit (capecitabine) (ODB formulary)

trastuzumab
New Drug Funding Program (Trastuzumab (Biosimilar) - Second Line - Metastatic Breast Cancer) (NDFP Website)

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B - Drug Regimen

Note: Different trastuzumab products are **not interchangeable**.

capecitabine	1000-1250* mg /m²	PO	BID, Days 1 to 14

(Outpatient prescription in multiples of 150mg or 500mg tablets)

*May use 1000 mg/m^2 BID Days 1 to 14 in heavily pretreated patients. Health Canada approved dose is 1250 mg/m^2 BID Days 1 to 14

trastuzumab	8 mg /kg	IV loading dose	Day 1 (cycle 1)

followed by (starting cycle 2):

trastuzumab	6 mg /kg	IV maintenance dose	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

• Topical emollients (e.g. hand creams, udder balm) therapy may ameliorate the manifestations of hand-foot syndrome in patients receiving capecitabine.
• Supportive care should be provided, including loperamide for diarrhea.

• To prevent recurrence of infusion-associated reactions with trastuzumab, acetaminophen and diphenhydramine may be given as pre-medication. Refer to the Trastuzumab drug monograph for full

details.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Capecitabine:

Do not start treatment with capecitabine unless baseline neutrophil counts are ≥ 1.5 x 10^9/L and/or platelet counts of ≥ 100 x 10^9/L. Patients should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Supportive care should be provided, including loperamide for diarrhea. Doses should not be re-escalated if reduced for toxicity. Missed or omitted doses of capecitabine should not be replaced.

Dose modifications are mandatory for gastrointestinal, dermatological toxicity, neurotoxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Toxicity	Action During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2 1st appearance 2nd appearance 3rd appearance 4th appearance	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 100% 75% 50% --

Grade 3 1st appearance 2nd appearance 3rd appearance, OR any evidence of Stevens-Johnson syndrome or Toxic epidermal necrolysis	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 75% 50% --
Grade 4 1st appearance, including SJS or TEN, OR cardiotoxicity OR acute renal failure	 Discontinue permanently OR If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to grade 0-1.	 Discontinue OR 50%
2nd appearance OR any occurrence of confirmed leukoencephalopathy	Discontinue permanently	--

Dosage in myelosuppression:

Modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Hematologic and Non-Hematologic Toxicities." Hold capecitabine during a treatment cycle in the presence of grade 3 or 4 hematologic toxicity.

Cardiotoxicity associated with trastuzumab:

Product Monograph Recommendations

- Trastuzumab should be held with a fall in LVEF (if LVEF falls ≥10 points from baseline and/or if LVEF falls to < 50%). Repeat LVEF in 3 weeks and consider discontinuing. Discontinue if clinically significant cardiac dysfunction or cardiac failure develops.

Canadian Consensus Guidelines: Discontinue if symptomatic.

Management of trastuzumab therapy in adjuvant breast cancer patients with asymptomatic decreases in LVEF (Mackey et al 2008):

Relationship of LVEF to Lower Limit of Normal (LLN)	Trastuzumab dose modification based on asymptomatic LVEF decrease from baseline		
	≤ 10 percentage points	**10-15 percentage points**	**≥ 15 percentage points**
Within facility's normal limits	Continue	Continue	**Hold** and repeat MUGA/ECHO after 4 weeks
1-5% below LLN	Continue [1]	**Hold** and repeat MUGA/ECHO after 4 weeks [1, 2]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]
≥ 6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks [3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]

[1] Consider cardiac assessment and starting ACEI therapy

[2] After 2 holds, consider permanent trastuzumab discontinuation

[3] Start ACEI therapy and refer to cardiologist

Hypersensitivity with trastuzumab:

Toxicity	Action
Mild hypersensitivity reaction	↓ infusion rate (and/ or hold) and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate. Consider premedication for next infusion.
Moderate hypersensitivity reaction	Hold and use beta-agonists, antihistamines, antipyretics, and/or corticosteroids as appropriate; complete infusion at ↓ rate if possible. Use premedication for next infusion.
Severe hypersensitivity reaction or Pulmonary Toxicity	Hold and manage symptoms aggressively with beta-agonists, antihistamines, antipyretics, and/or corticosteroids. Discontinue permanently and do not rechallenge

Hepatic Impairment

Capecitabine:

In patients with mild to moderate hepatic impairment, exposure is increased but no dose adjustment is necessary, although caution should be exercised. Use dose modification table above for increases in bilirubin. The use of capecitabine in patients with severe hepatic impairment has not been studied.

Trastuzumab:

No adjustment required.

Renal Impairment

Capecitabine:

Moderate renal impairment results in an increase in severe toxicity.

Creatinine Clearance (mL/min)	% of starting dose
51 - 80	100 % with close monitoring
30 - 50	75 % (use with caution)
<30	CONTRAINDICATED

Trastuzumab:

No adjustment required. The disposition of trastuzumab is not altered based on serum creatinine.

Dosage in the Elderly

Capecitabine:

No dose adjustment for the starting dose is required, but patients should be closely monitored and dose modification should be performed as described above. Older patients are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3 / 4 adverse effects, especially when used in combination.

Trastuzumab:

No adjustment required; the risk of cardiac dysfunction and myelosuppression may be increased in elderly patients. The reported trials did not determine differences in efficacy between patients > 65 years versus younger patients.

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F - Adverse Effects

Refer to capecitabine, trastuzumab, drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Hand-foot syndrome (may be severe)	• Diarrhea (may be severe) • Nausea, vomiting	• Mucositis • Increased LFTs (may be severe) • Fatigue • Musculoskeletal pain • Headache • Abdominal pain • Hot flashes	• Cardiotoxicity • Arrhythmia • Arterial / venous thromboembolism • Hypersensitivity • Rash • Myelosuppression +/- infection, bleeding • Leukoencephalopathy • GI perforation, obstruction • Idiopathic thrombocytopenic purpura • Eye disorders • Renal failure • Pancreatitis • Pneumonitis • Secondary malignancies • Dermatomyositis

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G - Interactions

Refer to capecitabine, trastuzumab drug monograph(s) for additional details

- Avoid concomitant administration of capecitabine with sorivudine or analogues given increased risk of capecitabine toxicity (may be fatal). Wait at least 4 weeks after sorivudine treatment before starting capecitabine.
- Avoid concomitant administration of capecitabine with phenytoin as capecitabine may increase phenytoin levels. Monitor phenytoin levels if co-administered.
- Caution and monitor INR/PT when co-administered with warfarin
- Caution and monitor for reduced effectiveness of capecitabine when co-administered with proton-pump inhibitors. Consider switching to an antacid if appropriate.
- Avoid concomitant administration of trastuzumab with anthracyclines and other cardiotoxic drugs. Use extreme caution with anthracyclines for up to 27 weeks after stopping trastuzumab.

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H - Drug Administration and Special Precautions

Refer to capecitabine, trastuzumab drug monograph(s) for additional details

Note: Different trastuzumab products are **not interchangeable**.

Administration: capecitabine

- Oral self-administration; drug available by outpatient prescription.
- Clinical studies performed with capecitabine administered 30 minutes after food. Administering capecitabine on an empty stomach may result in slightly higher exposure and thus toxicity.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package.

Administration: trastuzumab

- **NOTE:** Herceptin® (trastuzumab) and Kadcyla® (trastuzumab emtansine) are **NON-INTERCHANAGEABLE**. There have been fatal reports where the incorrect trastuzumab product was administered to patients with breast cancer in the clinical trials setting.
- Mix in 250 mL bag NS. Do not use D5W as it causes protein aggregation. Do not shake.
- Infuse loading dose IV over 90 minutes; subsequent infusions may be given over 30 minutes if the initial loading dose is well-tolerated.
- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- Should not be mixed or diluted with other drugs.
- Diluent supplied - Bacteriostatic Water for Injection (BWFI) - contains benzyl alcohol 1.1%; if patient is hypersensitive to benzyl alcohol, may reconstitute with Sterile Water for Injection, but must be used immediately and discard unused portion.
- Solution reconstituted with the supplied BWFI is stable up to 28 days refrigerated.
- Do not freeze the reconstituted solution.

Contraindications:

- Patients who have a known hypersensitivity to capecitabine, its excipients, or 5-fluorouracil
- Patients with known hypersensitivity to trastuzumab, Chinese Hamster Ovary (CHO) cell proteins, or any components of this product.
- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Concomitant use with sorivudine or related analogues (i.e. brivudine), given potential fatal drug interaction
- Trastuzumab should only be used in patients whose tumours overexpress HER2
- Patients with severe renal impairment (CrCl <30 mL/min)
- Capecitabine contains lactose; avoid in patients with hereditary galactose/glucose/lactase disorders

Precautions:

- Patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents
- Patients with a history of cardiovascular disease
- Patients with partial DPD deficiency - use with extreme caution. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- The risk of cardiotoxicity must be weighed against the potential benefits of treatment, especially in older patients, patients with pre-existing cardiac disease (including LVEF < 55%) and patients who have had prior cardiotoxic therapy. Note: in the adjuvant trials, patients with cardiac risk factors were excluded from the trials.
- Exercise caution in patients with pre-existing pulmonary disease or patients with extensive pulmonary tumour involvement, as they may experience more severe lung toxicities.
- Use with caution before or after anthracyclines (for up to 27 weeks after trastuzumab discontinuation due to long half-life).

Pregnancy & Lactation:

- These drugs are not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 7 months after the last dose.
- Breastfeeding is not recommended.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Cardiac assessment, including evaluation of left ventricular function (Echocardiogram or MUGA scan);; more frequent with asymptomatic reductions in LVEF; baseline, q3 months during treatment, then q6 months after trastuzumab discontinuation x2 years (and annually up to 5 years after last trastuzumab dose in adjuvant breast cancer patients who received anthracyclines), also as clinically indicated
- INR and/or PT; Baseline and regular if on anticoagulants
- Renal function tests; baseline and before each cycle
- Toxicity ratings of infusion-associated symptoms with trastuzumab (especially first infusion); Close monitoring at each visit
- Clinical toxicity assessment for diarrhea, dehydration, infection, bleeding, stomatitis, rash or hand-foot syndrome, cardiac failure, pulmonary, hepatic and neurotoxicity; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Liver function tests; Baseline and regular (if severe organ failure suspected)

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J - Administrative Information

Outpatient prescription for home administration (capecitabine)

Approximate Patient Visit	First cycle: 1.5 hours; Subsequent cycles: 0.5 hour
Pharmacy Workload (average time per visit)	19.589 minutes
Nursing Workload (average time per visit)	48.333 minutes

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K - References

Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol 2007;25(25):3853-8.

Capecitabine and trastuzumab drug monographs, Cancer Care Ontario.

Ishida T, Kiba T, Takeda M, et al. Phase II study of capecitabine and trastuzumab combination chemotherapy in patients with HER2 overexpressing metastatic breast cancers resistant to both anthracyclines and taxanes. Cancer Chemother Pharmacol 2009;64(2):361-9.

Schaller G, Fuchs I, Gonsch T, et al. Phase II study of capecitabine plus trastuzumab in human epidermal growth factor receptor 2 overexpressing metastatic breast cancer pretreated with anthracyclines or taxanes. J Clin Oncol. 2007;25(22):3246-50.

April 2023 Updated DPD deficiency information in the Dose Modifications and Special Precautions sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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