XELOX Regimen
Capecitabine (Xeloda®)-Oxaliplatin

Disease Site
- Gastrointestinal - Colorectal
- Gastrointestinal - Small bowel and appendix

Intent
Adjuvant

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 the adjuvant treatment of stage III and high risk stage II colorectal, small bowel or appendiceal cancer

Supplementary Public Funding
oxaliplatin
New Drug Funding Program (Oxaliplatin - Adjuvant Colorectal Small Bowel or Appendiceal Cancer) (NDFP Website)

capcitabine
ODB - General Benefit (capcitabine) (ODB Formulary)
B - Drug Regimen

oxaliplatin 130 mg /m² IV Day 1

capecitabine 1000 mg /m² PO BID, Days 1 to 14
(Outpatient prescription in 150mg and 500mg tablets)

C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a total of 8 cycles unless disease progression or unacceptable toxicity occurs

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate
No routine prophylaxis for capecitabine

Febrile Neutropenia Risk: Low

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.

Also refer to CCO Antiemetic Recommendations.

E - Dose Modifications

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

Use capecitabine with extreme caution in patients with partial DPD deficiency; reduce the initial dose substantially, monitor frequently and adjust the dose for toxicity as recommended in the dosage with toxicity section. In patients with unrecognized DPD deficiency, acute, life-threatening toxicity...
may occur; discontinue if acute grade 2-4 toxicity develops.

**Dosage with toxicity**

Do not retreat until ANC ≥ 1.5 x 10^9 /L, platelet counts ≥ 75-100 x 10^9 /L and major organ toxicity has resolved to ≤ grade 1. Doses should not be re-escalated if reduced for toxicity.

**Oxaliplatin**

Neurotoxicity was graded based on the following scales in some adjuvant colorectal cancer trials.

<table>
<thead>
<tr>
<th>Neurotoxicity Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No change</td>
</tr>
<tr>
<td>2</td>
<td>Mild paresthesias, loss of deep tendon reflexes</td>
</tr>
<tr>
<td>3</td>
<td>Mild or moderate objective sensory loss, moderate paresthesias</td>
</tr>
<tr>
<td>4</td>
<td>Severe objective sensory loss or paresthesias that interfere with function</td>
</tr>
</tbody>
</table>

**Dose Modifications**

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Oxaliplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent^1 Grade 2 neurotoxicity</td>
<td>↓ 25%</td>
</tr>
<tr>
<td>Transient^1 Grade 3 neurotoxicity</td>
<td>↓ 25%</td>
</tr>
<tr>
<td>Persistent^1 Grade 3 neurotoxicity or any Grade 4 neurotoxicity</td>
<td>Discontinue</td>
</tr>
<tr>
<td>≥ Grade 3 GI toxicity (after prophylaxis) OR Grade 3 or 4 Platelets OR Grade 3 or 4 Neutropenia (including febrile neutropenia)*</td>
<td>↓ 25% *</td>
</tr>
<tr>
<td>Sepsis / septic shock</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Other ≥ grade 3 toxicity^2</td>
<td>Consider dose ↓</td>
</tr>
<tr>
<td>Pharyngolaryngeal dysesthesia</td>
<td>Hold; then increase duration of infusion to 6 hours^3</td>
</tr>
</tbody>
</table>
### Toxicity Grade (continued)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Oxaliplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Hold, investigate; discontinue permanently if confirmed.</td>
</tr>
<tr>
<td>PRES/RPLS or hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia</td>
<td>Discontinue permanently</td>
</tr>
</tbody>
</table>

1. Transient = >7 days - <1 cycle; persistent = ≥ 1 cycle
2. For skin toxicity, reduce capecitabine dose only (see table below)
3. If oxygen saturation is normal, an anxiolytic agent may be given

* Discontinue if sepsis / septic shock

### Capecitabine

Mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening. Missed or omitted doses of capecitabine should not be replaced. In the clinical trial, capecitabine was continued in patients who discontinued oxaliplatin due to toxicity.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Action During a Course of Therapy</th>
<th>Capecitabine Dose Adjustment for Next Cycle (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1st appearance Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>2nd appearance Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>3rd appearance Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>4th appearance Discontinue treatment permanently</td>
<td>--</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1st appearance Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>2nd appearance Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>3rd appearance OR any evidence of Stevens-Johnson syndrome (i.e. sloughing) Discontinue treatment permanently</td>
<td>--</td>
</tr>
<tr>
<td>Toxicity (continued)</td>
<td>Action During a Course of Therapy</td>
<td>Capecitabine Dose Adjustment for Next Cycle (% of starting dose)</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st appearance</td>
<td>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.</td>
<td>Discontinue or 50%</td>
</tr>
<tr>
<td>2nd appearance</td>
<td>Discontinue permanently</td>
<td></td>
</tr>
</tbody>
</table>

### Hepatic Impairment

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>AST/ALT oxaliplatin (% previous dose)</th>
<th>capecitabine (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 x ULN</td>
<td>No change</td>
<td>Caution; use dose modification table above</td>
</tr>
<tr>
<td>&gt;2-4 x ULN and/or 2-4 x ULN</td>
<td>No change</td>
<td>Caution; use dose modification table above</td>
</tr>
<tr>
<td>&gt;4 x ULN and/or 4 x ULN</td>
<td>No data available</td>
<td>No data available</td>
</tr>
<tr>
<td>ANY or &gt; 4 X ULN</td>
<td>No data available</td>
<td>No data available</td>
</tr>
</tbody>
</table>

### Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>oxaliplatin (% previous dose)</th>
<th>capecitabine (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-80</td>
<td>No change</td>
<td>100%, with close monitoring</td>
</tr>
<tr>
<td>30-50</td>
<td>Caution</td>
<td>75 % (use with caution)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Discontinue</td>
<td>CONTRAINDIQUED</td>
</tr>
</tbody>
</table>
**Dosage in the Elderly**

For oxaliplatin, patients ≥ 65 years had a higher incidence of GI toxicity, myelosuppression, syncope and fatigue. No dose adjustments were needed but caution should be exercised.

For capecitabine, older patients are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3 / 4 adverse effects, especially when used in combination. Starting dosage adjustment is not recommended, but dose modifications should be performed for toxicity (see tables above).

**Dosage based on gender:**

Women may be at higher risk of severe (grades 3-4) neutropenia in adjuvant treatment of colorectal cancer. In metastatic colorectal cancer, females were observed to have higher number of severe adverse effects with oxaliplatin than men across all treatment arms.

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<table>
<thead>
<tr>
<th>Very common (≥ 50%)</th>
<th>Common (25-49%)</th>
<th>Less common (10-24%)</th>
<th>Uncommon (&lt; 10%), but may be severe or life-threatening</th>
</tr>
</thead>
</table>
| • Neuropathy (may be severe)  
• Myelosuppression +/- infection, bleeding (may be severe)  
• Nausea, vomiting  
• Hand-foot syndrome  
• Increased LFTs (may be severe)  
• Diarrhea (may be severe) | • Fatigue  
• Mucositis  
• Pharyngolaryngeal dysesthesia (with oxaliplatin)  
• Alopecia | • Constipation  
• Abdominal pain  
• Anorexia, weight loss  
• Edema  
• Musculoskeletal pain  
• Dysgeusia  
• Injection-site reactions (with oxaliplatin) | • Arterial thromboembolism  
• Venous thromboembolism  
• Hypersensitivity  
• Arrhythmia  
• Cardiotoxicity  
• GI obstruction, perforation  
• Hemolytic uremic syndrome  
• Hemolysis  
• Idiopathic |

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

- Use with warfarin increases the risk of bleeding as both drugs prolong INR. Caution, monitor INR and adjust warfarin dose as required.
- Avoid concomittant administration with phenytoin/fosphenytoin; capecitabine may increase levels. Monitor levels if must use together.
- Avoid leucovorin as this increases capecitabine toxicity
- Avoid concomittant administration of antacids containing aluminum or magnesium with capecitabine as these may increase absorption
- Avoid concomittant administration of sorivudine and analogues as these increase capecitabine toxicity. Wait 4 weeks after sorivudine treatment prior to starting capecitabine.
**Administration:**

**Oxaliplatin**
- May be mixed in 250-500 mL bag (D5W only - not NS, chloride containing or alkaline solutions) and given by slow infusion. Concentration must be between 0.2 to 0.7 mg/mL
- Infuse IV over 2 hours. Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia.
- Do not use with injection equipment containing aluminum, as this can degrade platinum compounds.
- Unopened vials should be stored at 15-30°C; protect from light.

**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 15°C to 30°C in the original package.

**Contraindications:**
- Patients who have a known hypersensitivity to capecitabine, its excipients, 5-fluorouracil, to oxaliplatin or other platinum agents (e.g. cisplatin)
- Patients with severe renal impairment (CrCl <30 mL/min)
- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) deficiency
- Concomitant use with sorivudine or related analogues (i.e. brivudine), given potential fatal drug interaction
- Capecitabine contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders.

**Other warnings/precautions:**
- Patients should be warned about cold avoidance prior to receiving oxaliplatin; ice for mucositis prophylaxis should not be used.
- Oxaliplatin may cause dizziness or visual disturbances in some patients; exercise caution when driving or operating machinery.
- Patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents

Refer to oxaliplatin, capecitabine drug monograph(s) for additional details.
Patients with a history of cardiovascular disease
Patients taking anticoagulants such as warfarin (see Drug Interactions section)
Use with extreme caution in patients with partial DPD deficiency

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
- Liver and renal function tests; Baseline and before each cycle
- Electrolytes, including magnesium; Baseline and regular
- INR and/or PT; Baseline and regular if on anticoagulants
- Clinical toxicity assessment of GI effects, neurotoxicity, infection, bleeding, thromboembolism, hypersensitivity, skin effects, respiratory and ophthalmic effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

J - Administrative Information

Outpatient prescription for home administration (capecitabine)

Approximate Patient Visit 2 hours
Pharmacy Workload (average time per visit) 17.14 minutes
Nursing Workload (average time per visit) 44.167 minutes

K - References

Capecitabine and oxaliplatin drug monographs, Cancer Care Ontario.

Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil


**PEBC Advice Documents or Guidelines**

- Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection
- Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer

**June 2019** Updated emetic risk category; added PEBC guideline link

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**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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