Systemic Therapy Update

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

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*For Health Professionals Who Care For Cancer Patients*

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# EDITOR'S CHOICE

## NEW PROGRAMS

The BCCA Provincial Systemic Therapy Program has approved the following new programs effective 1 December 2016:

**Leukemia/BMT:**

**Treatment of Chronic Myeloid Leukemia with Bosutinib (ULKCMLB) or Ponatinib (ULKCMLP)** – Bosutinib and ponatinib are new oral tyrosine kinase inhibitors (TKIs) that are now approved at the BCCA for the treatment of Chronic Myeloid Leukemia (CML) as per criteria outlined in the table below.

| | Bosutinib | Ponatinib |
|---|---|---|
| Chronic Phase<br>or<br>Accelerated Phase | ▪ Resistant to at least 2 prior TKIs, or<br>▪ Intolerant to imatinib, nilotinib and dasatinib<br>▪ Preferred over ponatinib | ▪ Resistant to at least 2 prior TKIs, or<br>▪ Intolerant to imatinib, nilotinib, dasatinib and bosutinib |
| Blast Phase | ---- | ▪ Resistant to at least 2 prior TKIs, or<br>▪ Intolerant to imatinib and dasatinib |
| T315I Mutation Positive | ---- | ▪ No prior TKI requirements |

Approval of the above treatment programs are based on two non-comparative studies. In the SKI-200 study, bosutinib demonstrated high rates of major cytogenic response (MCyR) (32% to 59%), a 2-year

progression free survival (PFS) rate of 81%, and a 2-year overall survival (OS) rate of 91%.[1] Bosutinib was also associated with higher quality of life measures across a number of scales. In the PACE study, ponatinib also yielded high MCyR rates (23% to 56%) and 12-month OS rates ranging from 29% (blast phase) to 94% (chronic phase).[2]

**Treatment of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) with Ponatinib (ULKCMLP)** – In addition to the above indications, ponatinib is also approved for the treatment of Ph+ ALL as per criteria outlined in the table below.

| | Ponatinib |
|---|---|
| Ph+ ALL | ▪ Resistant to <u>at least</u> 2 prior TKIs, or<br>▪ Intolerant to imatinib and dasatinib |
| T315I Mutation Positive | ▪ No prior TKI requirements |

The PACE study also included a small group of patients (7%) with Ph+ ALL. In these patients, ponatinib also demonstrated a high MCyR rate (47%) and a 12-month OS rate of 40%.[2]

*Toxicities:*

Bosutinib is generally well tolerated. It has a unique toxicity profile compared to other TKIs consisting mainly of gastrointestinal adverse effects (nausea, vomiting, diarrhea), rash and myelosuppression. These can be successfully managed with dose interruptions and/or reductions. For further information about the toxicities and pharmacology of bosutinib, please see the *Cancer Drug Manual* section below.

Ponatinib, on the other hand, is associated with significant toxicities, including thrombocytopenia, rash, dry skin and abdominal pain. Serious adverse effects include arterial thromboembolic and arterial stenosis events, hemorrhage, cardiac failure, pancreatitis and pneumonia. To ensure careful surveillance and management of patients receiving ponatinib, the drug is only available through the *ICLUSIG™ Controlled Distribution Program*. Requirements under this program include:

- Only prescribers and pharmacists registered with the program are able to prescribe and dispense ponatinib.
- Prescribers must be certified by and meet all requirements of the program in order to prescribe ponatinib.

Further information about the *ICLUSIG™ Controlled Distribution Program* is available at www.iclusigcdp.ca. For information about the pharmacology of ponatinib, please see the *Cancer Drug Manual* section below.

**<u>Lymphoma</u>:**

**Siltuximab for the Treatment of Multicentric Castleman's Disease (ULYSILTUX)** – Multicentric Castleman's Disease (MCD) is a rare and heterogeneous group of lymphoproliferative disorders characterized by lymphadenopathy and systemic symptoms (e.g. fever, night sweats, fatigue, anorexia, cachexia). Elevated levels of interleukin-6 (IL-6) are thought to be associated with the pathogenesis of MCD. A subset of MCD patients is negative for the human immunodeficiency virus (HIV) and the human herpesvirus-8 (HHV-8). In this patient population, there were no previous randomized trials to establish the standard of care until now. Siltuximab is a chimeric immunoglobulin G1κ monoclonal antibody that targets human IL-6. In a randomized, placebo-controlled trial involving 79 patients with HIV negative, HHV-8 negative MCD,

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siltuximab was superior to placebo in the rates of durable tumour and symptomatic response (34% vs. 0%).[3] Durable tumour and symptomatic response was defined as a complete or partial response, along with improvement or stabilization of disease-related symptoms for at least 18 weeks during treatment.

Siltuximab is given intravenously every 3 weeks. Once symptom control is achieved, the dosing interval may be lengthened. Siltuximab is well tolerated, with the most common grade 3 and 4 toxicities being fatigue, night sweats and anemia. Infusion-related reactions may occur and can be minimized by premedicating with oral acetaminophen and diphenhydramine. Serious infections should be treated prior to siltuximab therapy as treatment may mask the signs and symptoms of an infection.

**Melanoma:**

**Single-Agent Trametinib for BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma (USMAVTRA)** – Trametinib monotherapy is now approved as an additional treatment option for first-line treatment or second-line treatment following previous therapy with checkpoint inhibitors (pembrolizumab, ipilimumab). While combination therapy with trametinib and dabrafenib (USMAVDT) followed by a BRAF inhibitor alone (dabrafenib, vemurafenib) remains the preferred treatment in this setting, trametinib monotherapy (a mitogen-activated extracellular kinase [MEK]-targeted agent) is available for patients with a contraindication to either a BRAF inhibitor alone or combination BRAF/MEK-targeted therapy.

In a phase III open-label trial (METRIC), trametinib demonstrated superior median PFS (4.8 months) compared to chemotherapy with either dacarbazine or paclitaxel (1.5 months), with a hazard ratio of 0.45 (95% CI 0.33-0.63).[4] The median OS had not yet been reached, but the 6-month OS was superior with trametinib despite a 47% crossover rate (81% vs. 67%, HR 0.54 [95% CI 0.32-0.92]). The most common adverse effects reported with trametinib were rash, diarrhea and peripheral edema. Rare, but serious, cardiac and ocular toxicities have also been reported. Recommendations on the monitoring and management of these toxicities can be found in the USMAVTRA treatment protocol.

References:
1. pCODR Final Clinical Guidance Report: Bosutinib (Bosulif) for chronic myelogenous leukemia. Apr 21, 2015.
2. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013;369: 1783-1796.
3. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomized, double-blind, placebo-controlled trial. Lancet Oncol 2014;15:966-974.
4. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. NEJM 2012;367:107-114.

## PROVINCIAL SYSTEMIC THERAPY PROGRAM

### BCCA FLU VACCINE GUIDELINE

A new **BCCA Flu Vaccine Guideline** is now available on the BCCA website at: http://www.bccancer.bc.ca/health-professionals/professional-resources/cancer-management-guidelines/supportive-care.

Highlights of this guidelines include:

- Patients on active chemotherapy, immunotherapy or radiation therapy can receive influenza

immunization with an INACTIVATED vaccine unless contraindicated
- These patients should NOT receive live attenuated vaccines such as the intranasal form of the influenza vaccine (e.g. FluMist®)
- Specific recommendations on the timing of influenza immunization
- Specific recommendations for patients receiving checkpoint inhibitors (e.g. ipilimumab, pembrolizumab, nivolumab)

## CANCER DRUG MANUAL

### NEW MONOGRAPHS AND PATIENT HANDOUTS

**Bosutinib Monograph** and **Patient Handout** have been developed, with expert review provided by Dr. Donna Forrest (hematologist) and Judith Nyrose (pharmacist) of the BCCA Leukemia/BMT tumour group. Bosutinib is a second-generation tyrosine kinase inhibitor (TKI) that specifically targets BCR-ABL and Src kinases. The recommended daily dose is 500 mg orally with food. Grapefruit and grapefruit juice should be avoided during treatment as they may increase bosutinib toxicity by inhibiting CYP3A4-mediated metabolism. Clinically significant side effects include infections, diarrhea, nausea and vomiting, and increased risk of fractures. Because QT-prolongation and electrolyte disturbances have been observed, electrolyte abnormalities should be corrected prior to treatment, and ECG and electrolytes monitoring during treatment is indicated. Bosutinib is contraindicated in patients with hepatic impairment at baseline due to a higher risk of QT-prolongation. Hypersensitivity reactions, which may be caused by excipients in the tablets, have been reported.

**Ponatinib Monograph** and **Patient Handout** have been developed, with expert review provided by Dr. Donna Forrest (hematologist) and Judith Nyrose (pharmacist) of the BCCA Leukemia/BMT tumour group. Ponatinib is a TKI with activity against wild-type and mutant BCR-ABL kinase, as well as VEGF, platelet-derived growth factor receptor, KIT, ephrin and RET. Ponatinib is more potent *in vitro* than imatinib against wild-type BCR-ABL. The recommended dosing is 45 mg orally once daily, with or without food. Grapefruit and grapefruit juice should be avoided during treatment as they may increase ponatinib toxicity by inhibiting CYP3A4-mediated metabolism. For information about the toxicity profile of ponatinib and the ICLUSIG® Controlled Distribution Program, please see the *Editor's Choice* section above.

### REVISED MONOGRAPHS AND PATIENT HANDOUTS

Highlights of key changes and/or updates to the Monographs and Patient Handouts are listed below:

**Bevacizumab Monograph:**
- *Special Precautions* and *Side Effects* table – information on osteonecrosis of the jaw added

**Bortezomib Monograph:**
- *Special Precautions* – information on Herpes zoster reactivation added
- *Solution Preparation and Compatibility* section – reconstitution directions clarified to explain the reason for using 1 mg/mL dilution for both IV and SC administration

## CANCER DRUG MANUAL

**Filgrastim Monograph:**

- *Parenteral Administration* and *Dosing* – emphasized subcutaneous (SC) as the preferred route
- *Supply and Storage* – prefilled syringes added

**Fluorouracil Chemotherapy Preparation and Stability Chart:**

- Stability information for Accord brand updated

**Fulvestrant Monograph:**

- *Interactions* – immunoassay interaction added (may result in falsely elevated estradiol levels which can affect treatment decisions)
- *Parenteral Administration* table and *Dosing* – wording regarding site of injection clarified

**Oxaliplatin Monograph** and **Chemotherapy Preparation and Stability Chart:**

- *Supply and Storage* – Sandoz brand added

### EDITORIAL BOARD MEMBERSHIP

The Cancer Drug Manual Team would like to bid farewell to Sylvi LeBlanc (Registered Nurse, Sindi Ahluwalia Hawkins Centre for the Southern Interior) as she steps down from the Cancer Drug Manual Editorial Review Board in pursuit of other opportunities. The team would like to thank Sylvi for her many contributions to the Cancer Drug Manual during her years of service and wish her all the best in her future endeavours.

## BENEFIT DRUG LIST

### NEW PROGRAMS

Effective 1 December 2016, the following BCCA treatment programs have been added to the BCCA Benefit Drug List:

| Protocol Title | Protocol Code | Benefit Status |
|---|---|---|
| Treatment of Chronic Myeloid Leukemia Using Bosutinib | ULKCMLB | Restricted |
| Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia Using Ponatinib | ULKCMLP | Restricted |
| Treatment of Multicentric Castleman's Disease (MCD) Negative for Human Immunodeficiency Virus (HIV) and Human Herpes Virus-8 (HHV-8) Using Siltuximab | ULYSILTUX | Restricted |
| Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma Using Trametinib | USMAVTRA | Restricted |

## List of New and Revised Protocols, Pre-Printed Orders and Patient Handouts

**BC Cancer Agency Protocol Summaries, Provincial Pre-Printed Orders (PPPOs) and Patient Handouts** are revised periodically. New, revised or deleted protocols, PPPOs and patient handouts for this month are listed below. Protocol codes for treatment requiring BCCA Compassionate Access Program approval are prefixed with the letter "U".

**NEW Protocols, PPPOs and Patient Handouts (Affected Documents are Checked)**

| CODE | Protocol | PPPO | Patient Handout | Protocol Title |
|---|---|---|---|---|
| **ULKCMLB** | ☑ | ☑ | ☐ | Treatment of Chronic Myeloid Leukemia Using Bosutinib |
| **ULKCMLP** | ☑ | ☑ | ☐ | Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia Using Ponatinib |
| **ULYSILTUX** | ☑ | ☑ | ☐ | Treatment of Multicentric Castleman's Disease (MCD) Negative for Human Immunodeficiency Virus (HIV) and Human Herpes Virus-8 (HHV-8) Using Siltuximab |
| **USMAVTRA** | ☑ | ☑ | ☑ | Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma Using Trametinib |

**REVISED Protocols, PPPOs and Patient Handouts (Affected Documents are Checked)**

| CODE | Protocol | PPPO | Patient Handout | Changes | Protocol Title |
|---|---|---|---|---|---|
| **UGIYTT** | ☑ | ☐ | ☐ | *Eligibility clarified* | Yttrium-90 for Transarterial Radioembolisation (TARE) |
| **GOTDEMACO** | ☑ | ☑ | ☐ | *Tests clarified* | Therapy for High-Risk Gestational Trophoblastic Neoplasia (GTN) Using Etoposide, Methotrexate, Leucovorin (Folinic Acid), DACTINomycin, Cyclophosphamide and vinCRIStine |
| **LUAVERL** | ☑ | ☐ | ☐ | *Eligibility clarified* | Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with Erlotinib |
| **LUAVGEFF** | ☑ | ☐ | ☐ | *Eligibility clarified* | First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Gefitinib |
| **LUAVPG** | ☐ | ☐ | ☑ | *Typo corrected* | Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with Platinum and Gemcitabine |
| **UMYLENDEX** | ☑ | ☑ | ☐ | *Requirements for LFTs clarified* | Therapy of Multiple Myeloma Using Lenalidomide with Dexamethasone |
| **UMYLENMTN** | ☑ | ☑ | ☐ | *Requirements for LFTs clarified* | Maintenance Therapy of Multiple Myeloma Using Lenalidomide |
| **UMYPOMDEX** | ☑ | ☑ | ☐ | *Requirements for LFTs clarified* | Therapy of Multiple Myeloma Using Pomalidomide with Dexamethasone |

## Website Resources and Contact Information

| Website Resources | www.bccancer.bc.ca |
|---|---|
| Systemic Therapy Update | www.bccancer.bc.ca/health-professionals/professional-resources/systemic-therapy/systemic-therapy-update |
| Reimbursement & Forms: Benefit Drug List, Class II, Compassionate Access Program | www.bccancer.bc.ca/health-professionals/professional-resources/systemic-therapy |
| Cancer Drug Manual | www.bccancer.bc.ca/health-professionals/professional-resources/cancer-drug-manual |
| Cancer Management Guidelines | www.bccancer.bc.ca/health-professionals/professional-resources/cancer-management-guidelines |
| Cancer Chemotherapy Protocols, Pre-Printed Orders, Protocol Patient Handouts | www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols |
| Systemic Therapy Program Policies | www.bccancer.bc.ca/health-professionals/professional-resources/systemic-therapy |
| CON Pharmacy Educators | www.bccancer.bc.ca/health-professionals/professional-resources/pharmacy |

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| Education Resource Nurse | 604-877-6000 x 672638 | | nursinged@bccancer.bc.ca |
| Library/Cancer Information | 604-675-8003<br>Toll Free 888-675-8001 x 8003 | | requests@bccancer.bc.ca |
| Pharmacy Professional Practice | 604-877-6000 x 672247 | | mlin@bccancer.bc.ca |
| Nursing Professional Practice | 604-877-6000 x 672623 | | ilundie@bccancer.bc.ca |
| OSCAR | 888-355-0355 | 604-708-2051 | oscar@bccancer.bc.ca |
| Compassionate Access Program (CAP) | 604-877-6277 | 604-708-2026 | cap_bcca@bccancer.bc.ca |
| Pharmacy Chemotherapy Certification | 250-712-3900 x 686741 | | rxchemocert@bccancer.bc.ca |
| BCCA-Abbotsford Centre | 604-851-4710<br>Toll Free 877-547-3777 | | |
| BCCA-Centre for the North | 250-645-7300<br>Toll Free 888-775-7300 | | |
| BCCA-Fraser Valley Centre | 604-930-2098<br>Toll Free 800-523-2885 | | |
| BCCA-Sindi Ahluwalia Hawkins Centre for the Southern Interior | 250-712-3900<br>Toll Free 888-563-7773 | | |
| BCCA-Vancouver Centre | 604-877-6000<br>Toll Free 800-663-3333 | | |
| BCCA-Vancouver Island Centre | 250-519-5500<br>Toll Free 800-670-3322 | | |

## Editorial Review Board