Systemic Therapy Update

BC Cancer Agency
CARE + RESEARCH
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For Health Professionals Who Care For Cancer Patients

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EDITOR'S CHOICE

DRUG UPDATE – SHORTAGE OF VINORELBINE AND PARENTERAL SODIUM BICARBONATE

VINORELBINE

Vinorelbine is used as single agent and in combination chemotherapy for several tumour sites. Currently, there is very limited supply of vinorelbine because of production delays at the level of the manufacturer. Vinorelbine continues to be available on allocation from the manufacturer until the projected date of release of 17 July. BCCA Pharmacy has enough supply for current patients until the expected release date. If vinorelbine is not available, the following recommended alternatives can be considered:

1. LUAJNP - Adjuvant cisplatin and vinorelbine following resection of non-small cell lung cancer

ALTERNATIVE REGIMENS[1,2]	DOSING REGIMENS	NOTES
Cisplatin and gemcitabine[3,4]	Per LUAVPG	Reimbursed by BCCA for this indication during the vinorelbine shortage (CAP not required). Code as LUNOS.
Cisplatin and pemetrexed[5,6]	Per LUAVPP	
Carboplatin and paclitaxel	LUAJPC	Carboplatin may be less effective than cisplatin in the adjuvant setting. Hence, this is only an alternative in patients ineligible for LUAJNP and other cisplatin based regimens.

2. Other vinorelbine protocols:

VINORELBINE PROTOCOLS	ALTERNATIVE PROTOCOLS
Breast	
BRAVNAV	UBRAVERIB (CAP not required during shortage)
BRAVTRVIN	BRAVTRAP (or with weekly paclitaxel – CAP approval required)
Gynecological	
GOOVVIN	GOOVETO
Head & Neck	
HNSAVNP	HNSAVFAC, HNSAVFUP, HNSAVPAC, or HNNAVPPC
Lung	
LUAVNP	Other doublets
LUAVVIN	LUAVPG, but omitting cisplatin/carboplatin
LUMMVIN	If able to tolerate cisplatin, LUMMPG, LUMMPP

REFERENCES:

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer. Version 7.2015. 11 June 2015. Available at: https://www.tri-kobe.org/nccn/guideline/lung/english/non_small.pdf.
2. Kris MG, et al. Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non–small- cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario clinical practice guideline update. Published online: 24 April 2017.
3. Tibaldi C, et al. Cisplatin plus gemcitabine as adjuvant chemotherapy for radically resected non-small-cell lung cancer: a pilot study. Clin Lung Cancer 2009;10(1):53-7.
4. Barlesi F, et al. A randomized trial comparing adjuvant chemotherapy with gemcitabine plus cisplatin with docetaxel plus cisplatin in patients with completely resected non-small-cell lung cancer with quality of life as the primary objective. Interact Cardiovasc Thorac Surg 2015;20(6):783-90.
5. Schmid-Bindert G, et al. A randomized Phase 2 study of pemetrexed in combination with cisplatin or carboplatin as adjuvant chemotherapy in patients with completely resected stage IB or II non-small-cell lung cancer. Lung Cancer 2015;90(3):397- 404.
6. Kreuter M, et al. Three-year follow-up of a randomized phase ii trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine (the TREAT Study). J Thorac Oncol 2016;11(1):85-93.

PARENTERAL SODIUM BICARBONATE

There is a worldwide shortage of parenteral sodium bicarbonate and this has been compounded by a recent recall of some existing supplies due to possible microbial contamination in the manufacturing process. At this time, projected date of limited release is early August. Sodium bicarbonate is added to hydration in treatment protocols with higher doses of methotrexate (see table below) to alkalinize the urine, thereby preventing renal toxicity. Alkalinization can increase the solubility of methotrexate and reduce its precipitation in the renal tubules and collecting ducts.

LYCHOPRMTX	Central nervous system prophylaxis with high dose methotrexate, CHOP and rituximab in diffuse large B-cell lymphoma
LYCODOXMR	Treatment of Burkitt lymphoma and leukemia with cyclophosphamide, vincristine, doxorubicin, methotrexate, leucovorin and rituximab
LYHDMRP	Treatment of primary intracerebral lymphoma with high dose methotrexate and rituximab
LYHDMTXP	Treatment of primary intracerebral lymphoma with high dose methotrexate
LYHDMTXR	Treatment of leptomeningeal lymphoma or recurrent intracerebral lymphoma with high dose methotrexate
MOHDMTX	Treatment of meningeal disease (miscellaneous tumour origins) using high dose methotrexate with leucovorin rescue
SAHDMTX	Treatment of osteosarcoma using high dose methotrexate with leucovorin rescue
GOTDEMACO	Treatment of high risk gestational trophoblastic neoplasia using etoposide, methotrexate, leucovorin, dactinomycin, cyclophosphamide and vincristine
GOTDLR	Treatment of low risk gestational trophoblastic cancer using dactinomycin and methotrexate

The following alkalinizing regimens are recommended during the shortage:

For LYCHOPRMTX, LYCODOXMR, LYHDMRP, LYHDMTXP, LYHDMTXR, MOHDMTX and SAHDMTX Protocols

Current Treatment	**Recommended Alternative Treatment**
Pre-hydration and alkalinization IV 2/3 : 1/3 with sodium bicarbonate 100 mEq/L and potassium chloride 20 mEq/L at 125 mL/h for 4 hours pre-methotrexate	Pre-hydration IV 2/3 : 1/3 with potassium chloride 20 mEq/L at 125 mL/h for 4 hours pre-methotrexate
Alkalinization Oral sodium bicarbonate 3000 mg PO q4h (start on admission to hospital or at 0800 h on day planned for methotrexate if already in hospital) until methotrexate level less than 0.1 micromol/L	Alkalinization Oral sodium bicarbonate 3000 mg PO q4h (start on admission to hospital or at 0800 h on day planned for methotrexate if already in hospital) until methotrexate level less than 0.1 micromol/L *AND for at least 48 hours after methotrexate.* *Oral sodium bicarbonate will be optimized as much as possible, with anti-emetic support if needed*
Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than or equal to 7 before starting methotrexate	Check urine pH before starting methotrexate. If pH less than 7, *add sodium acetate 100 mEq/L to pre-hydration fluid.* ***NOTE: sodium acetate is also in short supply.***
Post-hydration and alkalinization IV 2/3 : 1/3 with sodium bicarbonate 100 mEq/L and potassium chloride 20 mEq/L at 125 mL/h for 48 hours after methotrexate	Post-hydration and alkalinization IV 2/3 : 1/3 with potassium chloride 20 mEq/L at 125 mL/h for 48 hours after methotrexate. *Continue oral sodium bicarbonate 3000 mg PO q4h* until methotrexate level less than 0.1 micromol/L *AND for at least 48 hours after methotrexate.*

EDITOR'S CHOICE

For GOTDEMACO Protocol

Current Treatment	Recommended Alternative Treatment
Post-hydration and alkalinization IV 2/3 : 1/3 with sodium bicarbonate 100 mEq/L and potassium chloride 20 mEq/L at 200 mL/h for 20 hours after the end of methotrexate infusion	Post-hydration and alkalinization IV 2/3 : 1/3 with potassium chloride 20 mEq/L at 200 mL/h for 20 hours after the end of methotrexate infusion *Oral sodium bicarbonate 3000 mg PO q4h for 20 hours after the end of methotrexate infusion, with anti-emetic support if needed.*

For GOTDLR Protocol

Current Treatment	Recommended Alternative Treatment
Pre-hydration and alkalinization IV 2/3 : 1/3 with sodium bicarbonate 100 mEq/L and potassium chloride 20 mEq/L at 200 mL/h until urine output at least 100 mL/h and urine pH greater than 7.	Pre-hydration and alkalinization IV 2/3 : 1/3 with potassium chloride 20 mEq/L at 200 mL/h until urine output at least 100 mL/h and urine pH greater than 7. *Oral sodium bicarbonate 3000 mg PO q4h (start on admission to hospital or at 0800 h of day planned for methotrexate if already in hospital) until urine pH greater than 7 AND for 20 hours after methotrexate. Oral sodium bicarbonate will be optimized as much as possible, with anti-emetic support if needed.*
Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than or equal to 7 before starting methotrexate.	Check urine pH before starting methotrexate. If pH less than 7, *add sodium acetate 100 mEq/L to pre-hydration fluid.* ***NOTE: sodium acetate is also in short supply.***
Post-hydration and alkalinization IV 2/3 : 1/3 with sodium bicarbonate 100 mEq/L and potassium chloride 20 mEq/L at 200 mL/h for 20 hours after methotrexate	Post-hydration and alkalinization IV 2/3 : 1/3 with potassium chloride 20 mEq/L at 200 mL/h for 20 hours after the end of methotrexate infusion *Continue oral sodium bicarbonate 3000 mg PO q4h for 20 hours after the end of methotrexate infusion*

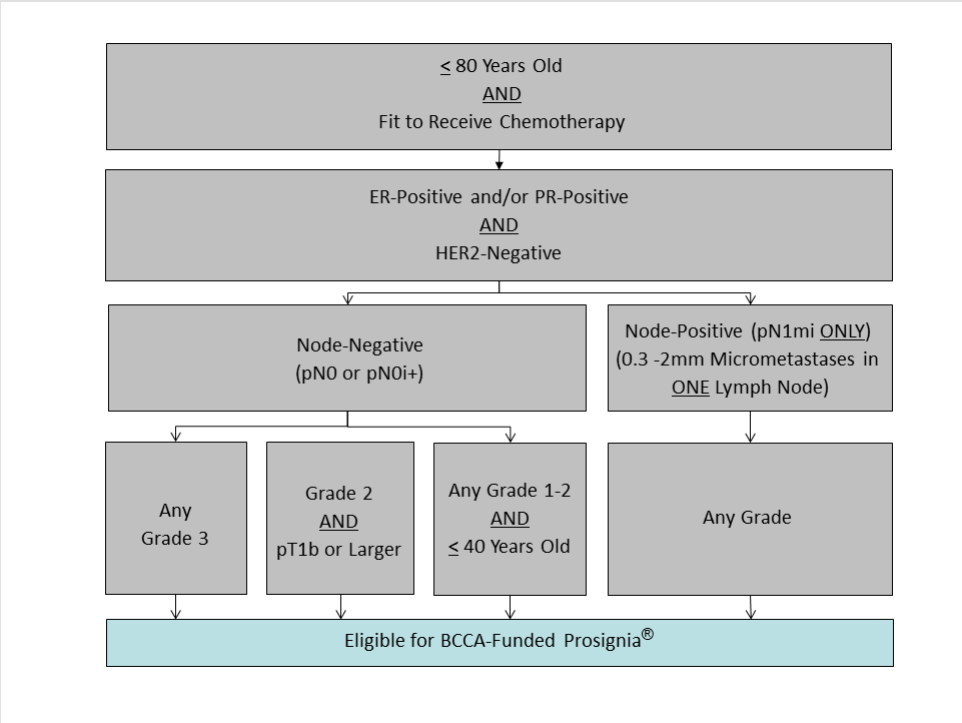
NEW PROGRAMS

Effective 1 July 2017, the BCCA Provincial Systemic Therapy Program has approved the following programs.

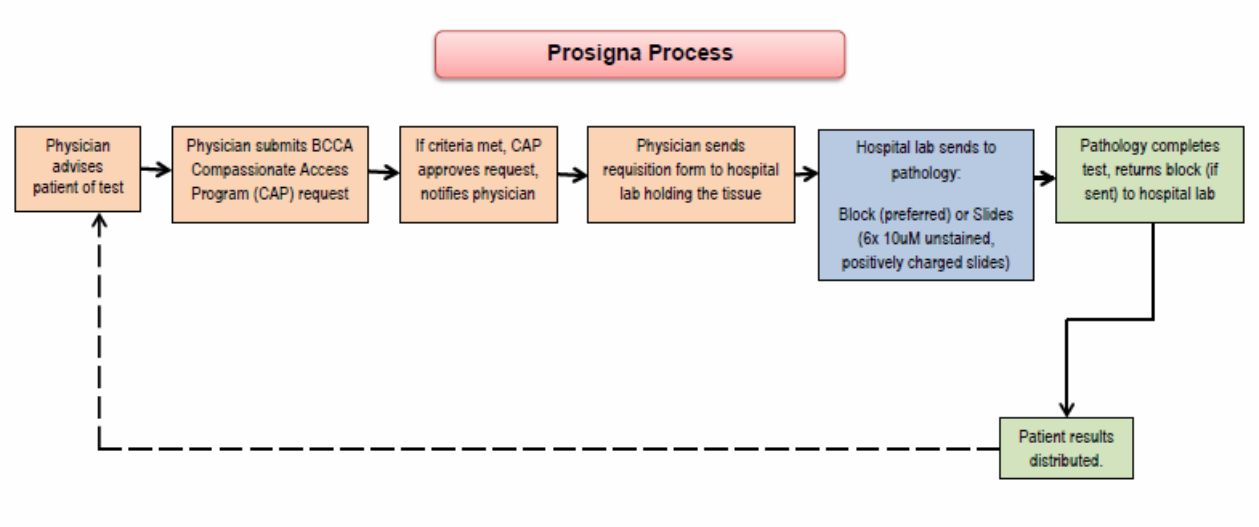
Breast:

Prosigna® Breast Cancer Assay in Hormone Receptor-Positive and Node-Negative Early Breast Cancer – This genomic assay is now available as a treatment decision-making tool for oncologists in determining the need of adjuvant chemotherapy. Note that patients can only be funded for Oncotype DX® or Prosigna®, but not both. It uses molecular prognostic profiling of 50 genes to estimate the 10-year recurrence risk of

breast cancer. Prosigna® is performed at the BCCA Laboratory Services and the turnaround time is about 10 working days (or two weeks) from the time the specimen has been received by the lab. The patient eligibility is the same as with Oncotype DX®:



A Compassionate Access Program (CAP) approval is needed for Prosigna® testing. More details on the request process are available on: www.bccancer.bc.ca/health-professionals/professional-resources/laboratory-services.



Reference:
Dowsett M, et al. Comparison of PAM 50 risk of recurrence score with Oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol 2013;31(22):2783-90.

REVISED PROGRAMS

EDITOR'S CHOICE

The BCCA Provincial Systemic Therapy Program has revised the following program effective 1 July 2017:

Leukemia:

Azacitidine Therapy of Myelodysplastic Syndrome (ULKMDSA) has been expanded to include patients age 65 or older who are newly diagnosed with acute myeloid leukemia with intermediate or high risk cytogenetics and ineligible for intensive chemotherapy. In a phase III trial comparing azacitidine to conventional chemotherapy or supportive care in this population, there was an increased overall survival (10.4 vs. 6.5 mos, HR 0.85) with azacitidine.

Reference:
Dombret H, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 2015;126(3):291-9.

COMMUNITIES ONCOLOGY NETWORK (CON)

CON REFERRAL POLICY AND WEB FORM

The CON Referral (CONRef) form and policy (Systemic Therapy Policy III-110) have been updated. Starting 4 July, you will see slight modifications to the referral form, which will link to the updated policy and answers to frequently asked questions about the changes. These changes will clarify responsibilities and improve communication between care providers, so to continue to provide the best care possible to the patients.

The CONRef system is a secure online web-based system that facilitates the delegation and transfer of care from a BC Cancer Agency (BCCA) regional centre to a CON clinic responsible for delivering an element of that care. The CONRef referral form indicates the treatment plan for the patients, thus allowing for the safe administration of systemic and chemotherapy closer to home. The associated CON referral Policy III-110 describes the minimum required process steps for transferring care from a BCCA medical oncologist or radiation oncologist to CON clinic staff.

BENEFIT DRUG LIST

NEW PROGRAMS

Effective 16 June 2017, the following drug has been added to the BCCA Benefit Drug List:

Drug	Indication	Protocol Code	Benefit Status
Plerixafor	Hematopoietic stem cell mobilization	**Plerixafor**	Class I

CONTINUING EDUCATION CORNER

ANNUAL BEST OF ASCO® 2017 – VANCOUVER

Date: Friday, 7 July 2017
Location: Westin Bayshore, Vancouver, BC
Website: www.regonline.ca/boav2017
Registration: $179 (Physicians), $95 (Nurses, Trainees and Allied Health Professionals)

The Annual Best of ASCO® aims to provide oncology healthcare practitioners with a summary of the most significant treatment advances presented at the 2017 Annual Meeting of the American Society of Clinical Oncology. Presentations from expert faculty across Western Canada will focus on several key disease sites from the perspective. For further information about the conference and its agenda, please visit the conference website noted above.

CANCER DRUG MANUAL

NEW MONOGRAPHS AND PATIENT HANDOUTS

The Siltuximab **Monograph** and **Patient Handout** have been developed with expert review provided by Alina Gerrie (medical oncologist) and Linda Hamata (pharmacist) of the BCCA Lymphoma & Myeloma Tumour Group. Siltuximab is the first approved treatment for HIV-negative and human herpes virus-8 negative Multicentric Castleman's disease (MCD). MCD is a rare lymphoproliferative disorder characterized by overproduction of interleukin-6 (IL-6) within the lymph nodes. Siltuximab is a human-murine chimeric monoclonal antibody that binds to human IL-6 and blocks the systemic manifestations due to overproduction of IL-6, such as inflammation, anemia, cachexia, and plasma cell proliferation. It is given as an 11 mg/kg intravenous infusion over 60 minutes every three weeks until treatment failure as per BCCA Protocol ULYSILTUX. The most common side effects of siltuximab are: pruritus, rash, edema, and upper respiratory tract infection. Serious side effects include infusion reactions, sepsis, and gastrointestinal perforation. Siltuximab masks the body's response to infection, so all active infections should be treated and resolved prior to treatment, and if an infection develops while on therapy, siltuximab should be held until the infection resolves. Protocol and PPPO are already on the BCCA website.

REVISED MONOGRAPHS AND PATIENT HANDOUTS

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

Everolimus and Temsirolimus Monographs

- *Side Effects:* added new paragraph about stomatitis

Dabrafenib and Trametinib Monographs

- *Uses:* added lung cancer as a new Health Canada approved indication
- *Dosing:* added new protocol USMAVDT

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".

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

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
BRAJCEFG	☐	☑	☐	*Reminder for filgrastim added*	Adjuvant Therapy for Breast Cancer Using Cyclophosphamide, Epirubicin, Fluorouracil and Filgrastim
UBRAJDAC	☐	☑	☐	*Reminder for filgrastim added*	Adjuvant Therapy for Breast Cancer Using Cyclophosphamide, DOXOrubicin and DOCEtaxel
BRAJDC	☐	☑	☐	*Reminder for filgrastim added*	Adjuvant Therapy for Breast Cancer Using DOCEtaxel and Cyclophosphamide
BRAJDCARBT	☐	☑	☐	*Reminder for filgrastim added*	AdjuvantTherapy for Breast Cancer Using DOCEtaxel, CARBOplatin, and Trastuzumab
BRAJDTFEC	☐	☑	☐	*Acetaminophen added for headache and rigors*	Adjuvant Therapy for Breast Cancer Using DOCEtaxel and Trastuzumab, and Fluorouracil, Epirubicin and Cyclophosphamide
BRAJTDC	☐	☑	☐	*Reminder for filgrastim added*	Adjuvant Therapy for Breast Cancer Using Trastuzumab, DOCEtaxel and Cyclophosphamide
BRAVCAP	☐	☐	☑	*Management of missed dose and sun exposure clarified*	Therapy of Metastatic Breast Cancer using Capecitabine
BRAVDCAP	☐	☐	☑	*Management of missed dose and sun exposure clarified*	Palliative Therapy for Metastatic Breast Cancer using DOCEtaxel and Capecitabine
BRAVGEM	☑	☐	☐	*Minor typo corrected*	Palliative Therapy for Metastatic Breast Cancer using Gemcitabine
BRAVGEMD	☑	☐	☐	*Drug interaction with warfarin updated*	Palliative Therapy for Metastatic Breast Cancer using Gemcitabine and DOCEtaxel
BRAVGEMP	☑	☐	☐	*Drug interaction with warfarin updated*	Palliative Therapy for Metastatic Breast Cancer using CISplatin and Gemcitabine
BRAVGEMT	☑	☐	☐	*Drug interaction with warfarin updated*	Palliative Therapy for Metastatic Breast Cancer using Gemcitabine and PACLitaxel
BRAVLHRHA	☐	☑	☐	*Return appointments clarified*	Therapy for Advanced Breast Cancer Using a LHRH Agonist and an Aromatase Inhibitor

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
BRAVPTRAD	☐	☑	☐	*Treatment and return appointments clarified*	Palliative Therapy for Metastatic Breast Cancer Using PERTuzumab, Trastuzumab (HERCEPTIN), and DOCEtaxel as First-Line Treatment for Advanced Breast Cancer
BRINFCEFG	☐	☑	☐	*Reminder for filgrastim added*	Therapy for Inflammatory Breast Cancer Using Cyclophosphamide, Epirubicin, Fluorouracil and Filgrastim
BRLACEFG	☐	☑	☐	*Reminder for filgrastim added*	Therapy for Locally Advanced Breast Cancer Using Cyclophosphamide, Epirubicin, Fluorouracil and Filgrastim
GIGAJCPRT	☐	☐	☑	*Minor typo corrected*	Adjuvant chemotherapy of gastric cancer patients with completely resected gastric cancer using Cisplatin, Capecitabine and Radiation Therapy
GIGAVCCT	☐	☑	☐	*Acetaminophen added for headache and rigors*	Palliative Treatment of Metastatic or Locally Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma Using CISplatin, Capecitabine and Trastuzumab (HERCEPTIN)
GIGAVCFT	☐	☑	☐	*Acetaminophen added for headache and rigors*	Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using CISplatin, Infusional Fluorouracil and Trastuzumab (HERCEPTIN)
GIGAVTR	☐	☑	☐	*Acetaminophen added for headache and rigors*	Continuation of Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Using Trastuzumab
ULKMDSA	☑	☐	☐	*Eligibility updated*	Therapy of Myelodysplastic Syndrome using azaCITIDine
SCESA	☑	☐	☐	*Skin reactions added as a precaution*	Guidelines for the Use of Erythropoiesis-Stimulating Agents (ESAs) in Patients with Cancer
USMAVDAB	☑	☑	☐	*Test and precautions updated*	Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma Using daBRAFenib
USMAVDT	☑	☑	☐	*Test, treatment, cycle length and precautions updated*	Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma Using daBRAFenib and Trametinib
USMAVNIV	☑	☐	☐	*Minor typo corrected*	Treatment of Unresectable or Metastatic Melanoma Using Nivolumab
USMAVTRA	☑	☑	☐	*Cycle length clarified*	Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma Using Trametinib

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, 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

Contact Information	Phone	Fax	Email
Systemic Therapy Update Editor			bulletin@bccancer.bc.ca
Provincial Systemic Therapy Program	604-877-6000 x 672247		mlin@bccancer.bc.ca
To update contact information of any CON sites, please contact:			bulletin@bccancer.bc.ca
Oncology Drug Information	604-877-6275		druginfo@bccancer.bc.ca
Education Resource Nurse	604-877-6000 x 672638		nursinged@bccancer.bc.ca
Library/Cancer Information	604-675-8003 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 Toll Free 877-547-3777		
BCCA-Centre for the North	250-645-7300 Toll Free 888-775-7300		
BCCA-Fraser Valley Centre	604-930-2098 Toll Free 800-523-2885		
BCCA-Sindi Ahluwalia Hawkins Centre for the Southern Interior	250-712-3900 Toll Free 888-563-7773		
BCCA-Vancouver Centre	604-877-6000 Toll Free 800-663-3333		
BCCA-Vancouver Island Centre	250-519-5500 Toll Free 800-670-3322		

Editorial Review Board