Provincial Health Services Authority

Systemic Therapy Update

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For Health Professionals Who Care for People with Cancer

Inside This Issue

Editor's Choice

New Programs

The BC Cancer Provincial Systemic Therapy Program has approved the following new treatment programs effective 01 April 2022. Full details of all treatment programs are available in the Chemotherapy Protocols section of the BC Cancer website.

Gastrointestinal

First-Line Atezolizumab and Bevacizumab for Advanced Hepatocellular Carcinoma (GIATZB) — The BC Cancer Gastrointestinal Tumour Group is introducing atezolizumab in combination with bevacizumab as an additional first-line treatment option for patients with advanced hepatocellular carcinoma (HCC) that is not amenable to curative or locoregional therapy. This is the first immune checkpoint inhibitor-VEGF inhibitor combination to be funded in the HCC patient population; historically, first-line treatment options consisted of sorafenib and lenvatinib.[1] Patients who started on first-line sorafenib (GISORAF) or lenvatinib (GILEN) prior to 01 April 2022 may switch to GIATZB if they have not experienced progression and meet all eligibility criteria. There is a small number of patients transitioning to GIATZB from the manufacturer patient assistance program; when patients begin receiving funded treatment at BC Cancer, they will be switched from brand name bevacizumab to biosimilar bevacizumab. If either atezolizumab or bevacizumab is discontinued due to intolerance, patients may continue with the remaining agent in the absence of progression.

Editor's Choice

New Programs

The use of atezolizumab plus bevacizumab in the first-line setting is supported by the phase III randomized, controlled IMbrave150 trial.[2,3] After a median follow-up of 15.6 months, statistically significant improvements in the co-primary end points of overall survival (OS) and progression-free survival (PFS) were demonstrated when compared with sorafenib monotherapy (median OS 19.2 months vs. 13.4 months, HR 0.66, 95% CI 0.52-0.85; median PFS 6.8 months vs. 4.3 months, HR 0.59, 95% CI 0.47-0.76). The most commonly reported any-grade treatment-related adverse events (trAEs) in the atezolizumab plus bevacizumab group were hypertension (23.7%), proteinuria (18.8%), fatigue (15.2%), elevated AST (14.0%), pruritus (13.1%) and infusion-related reaction (10.9%). The most common trAEs in patients receiving sorafenib were palmar-plantar erythrodysesthesia syndrome (48.1%), diarrhea (42.9%), hypertension (19.9%), reduced appetite (19.9%), rash (16.7%) and fatigue (15.4%).

Lung

First-Line Entrectinib for ROS1-Positive Advanced Non-Small Cell Lung Cancer (ULUAVENT) — The BC Cancer Lung Tumour Group is introducing entrectinib, a potent ROS1-inhibitor, as an alternative first-line treatment option for patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). ROS1 mutations occur in 1% to 2% of NSCLC cases and are more common in younger, female and non-smoking patients.[4] Approximately one-third of patients with advanced stage ROS1-positive NSCLC present with brain metastases at diagnosis; entrectinib was designed to penetrate the blood-brain barrier and be retained in the CNS. Patients who were started on, or had completed first-line chemotherapy and/or immunotherapy prior to 01 April 2022, may receive entrectinib if all other eligibility criteria are met. Crizotinib has been the standard first-line treatment for advanced ROS1-positive NSCLC; if crizotinib is discontinued for intolerable toxicity, patients may switch to entrectinib. BC Cancer Compassionate Access Program (CAP) approval is required.

The use of entrectinib in patients with advanced ROS1-positive NSCLC is supported by a pooled efficacy analysis of three phase I and II single-arm trials (ALKA, STARTRK-1 and STARTRK-2).[5] With a median follow-up of 15.5 months, the overall patient population achieved a median PFS of 19.0 months, as compared to 13.6 months for patients with baseline CNS disease. The median duration of response was longer among all responders as compared to patients with baseline CNS disease (24.6 months vs. 12.6 months). The majority of trAEs were grade 1 or 2, including dysgeusia (42%), dizziness (32%), constipation (33%), diarrhea (26%), fatigue (24%) and weight increase (19%). The most common grade 3 or 4 trAEs were weight increase (7%) and neutropenia (4%).

Lymphoma

Gemcitabine, Oxaliplatin and Pegaspargase for New, or Relapsed or Refractory, Natural Killer or T-Cell Lymphoma (LYGEMOXPEG) — The BC Cancer Lymphoma and Myeloma Tumour Group is implementing treatment with gemcitabine, oxaliplatin and pegaspargase for patients with newly diagnosed, or relapsed or refractory, natural killer (NK) or T-cell lymphoma (NK/T-cell lymphoma). NK/T-cell lymphoma is a rare and aggressive lymphoma with poor outcomes. BC Cancer funds LYSMILE, an inpatient treatment protocol for patients with newly diagnosed or relapsed or refractory disease. LYSMILE, however, is associated with significant toxicities such as grade 4 neutropenia in up to 92% of patients, nephrotoxicity, diarrhea, cardiotoxicity and mucositis.[6] LYGEMOXPEG is associated with less toxicity and can be delivered in the outpatient setting.

Editor's Choice

New Programs

The use of gemcitabine, oxaliplatin and pegaspargase in patients with newly diagnosed or relapsed or refractory NK/T-cell lymphoma is supported by a retrospective trial.[7] Patients received a median of five treatment cycles. Of patients with newly diagnosed disease, the overall response rate (ORR) was 78.9%, with a complete response (CR) rate of 42.1%. Similarly, of patients with relapsed or refractory disease, the ORR was 81.3% with a CR rate of 62.5%. Grade 3 or 4 neutropenia occurred in 40% of patients. Nonhematologic toxicities such as coagulation abnormalities and hepatic transaminase elevation were common, though most reported cases were mild in severity (grade 1 or 2).

Polatuzumab Vedotin, Bendamustine and Rituximab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LYPOLABR) — The BC Cancer Lymphoma and Myeloma Tumour Group is introducing polatuzumab vedotin in combination with bendamustine and rituximab (BR) for transplant-ineligible patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). Patients with relapsed or refractory DLBCL who are transplant-ineligible due to age or co-morbidities have limited treatment options, generally receiving single-agent or combination chemotherapy regimens that are associated with a median survival of less than 6 months.[8] Polatuzumab vedotin is a antibody-drug conjugate targeting CD79b, a component of the B-cell receptor signaling pathway that is expressed on all normal B cells and on most mature B-cell malignancies, including DLBCL.

The randomized phase II component of the GO29365 trial compared polatuzumab vedotin-BR with BR alone, in patients with transplant-ineligible DLBCL.[9] Patients received a median of 5 cycles, achieving a significantly higher PET-based CR rate with polatuzumab vedotin-BR (40% vs 17.5%). With median follow-up of approximately 22 months, median PFS and OS were also significantly improved in the polatuzumab vedotin-BR group (median PFS 9.5 months vs. 3.7 months, HR 0.36, 95% CI 0.21-0.63; median OS 12.4 months vs. 4.7 months, HR 0.42, 95% CI 0.24-0.75). Toxicities were mainly hematologic, with grade 3 or 4 rates slightly higher in the polatuzumab vedotin-BR group: neutropenia (46% vs. 33%), thrombocytopenia (41% vs. 23%) and anemia (28% vs. 18%). Peripheral neuropathy, which was low-grade and reversible, was notably more frequent in the polatuzumab vedotin-BR group (43.6% vs 7.7%). An extension cohort of additional patients was recently reported with comparable efficacy and safety, and persistent survival benefit.[10]

References

1. Pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC). Final recommendation for atezolizumab (Tecentriq®) for hepatocellular carcinoma. 17 November 2020.
2. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382(20):1894-1905. https://doi.org/10.1056/NEJMoa1915745
3. Finn RS, Qin S, Ikeda M, et al. IMbrave150: updated overall survival data from a global, randomized, open-label phase III study of atezolizumab + bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma. *J Clin Oncol* 2021;39(3_suppl):267-267. https://doi.org/10.1200/JCO.2021.39.3_suppl.267
4. Pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC). Final recommendation for entrectinib (Rozlytrek®) for ROS1-positive non-small cell lung cancer. 27 January 2021.
5. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21(2):261-270. https://doi.org/10.1016/S1470-2045(19)30690-4
6. Li X, Cui Y, Sun Z, et al. DDGP versus SMILE in newly diagnosed advanced natural killer/T-cell lymphoma: a randomized controlled, multicenter, open-label study in China. *Clin Cancer Res* 2016;22(21):5223-5228. https://doi.org/10.1158/1078-0432.CCR-16-0153
7. Wang J-H, Wang L, Liu C-C, et al. Efficacy of combined gemcitabine, oxaliplatin and pegaspargase (P-gemox regimen) in patients with newly diagnosed advanced stage or relapsed/refractory extranodal NK/T-cell lymphoma. *Oncotarget* 2016;7(20):29092-29101. https://doi.org/10.18632/oncotarget.8647
8. Pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC). Final recommendation for polatuzumab vedotin (Polivy®) for DLBCL. 21 April 2021.

Editor's Choice

New Programs

9. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol* 2020;38(2):155-165. https://doi.org/10.1200/JCO.19.00172
10. Sehn LH, Hertzberg M, Opat S, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. *Blood Adv* 2022;6(2):533–543. https://doi.org/10.1182/bloodadvances.2021005794

Cancer Drug Manual©

All documents are available in the Cancer Drug Manual© on the BC Cancer website.

New Documents

Note that the following drug is not BC Cancer Benefit Drug and requires application to the BC Cancer Compassionate Access Program (CAP). The corresponding Interim Monograph and Patient Handout are made available for reference only.

The **Binimetinib Interim Monograph** and **Patient Handout** have been developed with expert review provided by Dr. Vanessa Bernstein (medical oncologist) and Robert Tillmanns (pharmacist) of the BC Cancer Skin and Melanoma Tumour Group. Binimetinib is an orally administered inhibitor of mitogen-activated extracellular signal-regulated kinase (MEK inhibitor) used in combination with encorafenib in the treatment of melanoma. The usual dose of binimetinib is 45 mg twice daily.

Highlights from these documents include:

- cardiomyopathy can manifest as asymptomatic or symptomatic decreased ejection fraction
- retinal vein occlusion is a known class-related effect of MEK inhibitors; patients reporting new or worsening visual disturbances should be promptly referred for an eye exam
- cutaneous malignancies, including cutaneous squamous cell carcinoma and basal cell carcinoma, are reported; screen for suspicious lesions throughout treatment

Binimetinib has been added to the **Auxiliary Label List** and has been evaluated for the **BC Cancer Hazardous Drug List**.

The **Pegaspargase Monograph** has been developed with expert review provided by Dr. Jennifer Kendrick (clinical pharmacy specialist, BC Children's and Women's Hospital) and Carmen Mountford (clinical pharmacist, Leukemia/Bone Marrow Transplant Program, Vancouver General Hospital). Pegaspargase is a pegylated conjugate of L-asparaginase (*E. coli*-derived asparaginase, asparaginase *E. coli*) and is used in the treatment of acute lymphoblastic leukemia and natural killer or T-cell lymphoma. The usual dose of pegaspargase is 1500-2500 units/m^2 IV or IM, given in 3- or 4-week cycles depending on the protocol. Refer to protocols LYSMILE, LYASPMEDEX and LYGEMOXPEG.

Highlights from this document include:

- hypersensitivity reactions are common and can be life-threatening
- patients may develop neutralizing antibodies to pegaspargase, which can lead to hypersensitivity reactions and/or loss of effectiveness of treatment
- pegaspargase is associated with hepatotoxicity; pre-existing hepatic impairment is a risk factor

Cancer Drug Manual©

Revised Documents

Auxiliary Label List
Column one: added applicable Hazardous Drug labels for outpatient use

Atezolizumab Monograph
Uses: added liver cancer
Dosing: added new protocol (GIATZB)

Bevacizumab Monograph
Uses: added liver cancer
Dosing: added new protocol (GIATZB)

Carmustine Chemotherapy Preparation and Stability Chart
Updated available brands (added new Marcan brand; deleted Bristol brand as no longer available)

Entrectinib Monograph
Dosage Guidelines: bolded/italicized BC Cancer usual dose; added new protocol (ULUAVENT)

Mogamulizumab Chemotherapy Preparation and Stability Chart
Product stability: added extended stability per manufacturer

Nivolumab Chemotherapy Preparation and Stability Chart
Product column: added preparation information for undiluted product
Product stability: added extended stability per manufacturer; added note regarding light exposure at room temperature
Special Precautions: added note regarding particles

Pegaspargase Chemotherapy Preparation and Stability Chart
Drug column: updated name of manufacturer

Polatuzumab Vedotin Monograph
Dosage Guidelines: bolded/italicized BC Cancer usual dose; added new protocol (LYPOLABR)

Sacituzumab Govitecan Interim Monograph and **Chemotherapy Preparation and Stability Chart**
Supply and Storage: added new Canadian marketed brand (Gilead); revised Immunogenic brand information to differentiate the SAP supply from the new marketed supply; added target fill amount
Solution Preparation and Compatibility: added amount of overfill
Chemotherapy Preparation and Stability Chart: added new Canadian marketed brand (Gilead)

Vincristine Chemotherapy Preparation and Stability Chart
Product column: updated to include recommendation to protect bag from light during storage period

Drug Shortages

The following are updates of drug supply shortages in BC. Full details about new, updated or resolved drug shortages, including recommended treatment alternatives, are found in the *Briefing Notes* and email communications previously circulated to BC Cancer and the Community Oncology Network (CON).

Resolved

Paclitaxel NAB (ABRAXANE)

Adapted from BC Cancer email communication 18 March 2022

The manufacturing delays have been resolved and the 60% purchase allocation has been removed.

BC Cancer Benefit Drug List

New Programs

The following treatment programs have been added to the Benefit Drug List effective 01 April 2022:

Protocol Title	Protocol Code	Benefit Status
First-Line Treatment of Advanced Hepatocellular Carcinoma using **Atezolizumab** and **Bevacizumab**	**GIATZB**	Class I
First-Line Treatment of ROS1-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with **Entrectinib**	**ULUAVENT**	Restricted
Treatment of Newly Diagnosed or Relapsed/Refractory Natural Killer or T-Cell Lymphoma using **Gemcitabine**, **Oxaliplatin** and **Pegaspargase**	**LYGEMOXPEG**	Class I
Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Not Eligible for Transplant using **Polatuzumab Vedotin**, **Bendamustine** and **Rituximab**	**LYPOLABR**	Class I

Highlights of New & Revised Protocols, PPPOs and Patient Handouts

BC Cancer 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, with document revisions indicated in the respective columns. Protocol codes for treatment requiring BC Cancer Compassionate Access Program (CAP) approval are prefixed with the letter **U.**

NEW Protocols, PPPOs and Patient Handouts *(new documents checked ☑)*

Protocol Code	Protocol Title	Protocol	PPPO	Handout
GIATZB	First-Line Treatment of Advanced Hepatocellular Carcinoma using Atezolizumab and Bevacizumab	☑	☑	☑
ULUAVENT	First-Line Treatment of ROS1-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Entrectinib	☑	☑	☐
LYGEMOXPEG	Treatment of Newly Diagnosed or Relapsed/Refractory Natural Killer or T-Cell Lymphoma using Gemcitabine, Oxaliplatin and Pegaspargase	☑	☑	☑
LYPOLABR	Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Not Eligible for Transplant using Polatuzumab Vedotin, Bendamustine and Rituximab	☑	☑	☑

REVISED Protocols, PPPOs and Patient Handouts *(revisions in respective columns)*

Protocol Code	Protocol Title	Protocol	PPPO	Handout
BR | Breast				
BRAVGEMP	Palliative Therapy for Metastatic Breast Cancer using Cisplatin and Gemcitabine	-----	-----	*Handout title clarified*
CN | Neuro-Oncology				
CNAJTZRT	Concomitant (Dual Modality) and Adjuvant Temozolomide for Newly-Diagnosed Malignant Gliomas with Radiation	*Eligibility clarified*	-----	-----
CNMODPCV	Modified PCV Chemotherapy of Brain Tumours using Procarbazine, Lomustine (CCNU) and Vincristine	*Eligibility clarified*	-----	-----
GI | Gastrointestinal				
UGICABO	Treatment of Advanced Hepatocellular Carcinoma using Cabozantinib	*Eligibility and Exclusions updated*	-----	-----
GILEN	~~First-Line~~ Therapy of Advanced Hepatocellular Carcinoma using Lenvatinib	*Protocol title and Eligibility updated*	-----	-----
GIREGO	Treatment of Advanced Hepatocellular Carcinoma using Regorafenib	*Eligibility, Exclusions and Contact Physician updated*	-----	-----

REVISED Protocols, PPPOs and Patient Handouts *(revisions in respective columns)*

Protocol Code	Protocol Title	Protocol	PPPO	Handout
GISORAF	Therapy for Advanced Hepatocellular Carcinoma using Sorafenib ~~(NEXAVAR®)~~	*Protocol title, Contact Physician and Eligibility updated*	-----	-----
GO | Gynecologic				
GOTDEMACO	Treatment for High-Risk Gestational Trophoblastic Neoplasia (GTN) using Etoposide, Methotrexate, Leucovorin (Folinic Acid), Dactinomycin, Cyclophosphamide and Vincristine	*Tests clarified*	*Tests clarified*	-----
LK | Leukemia				
ULKMDSL	Therapy of Myelodysplastic Syndrome using Lenalidomide	*Tests clarified*	-----	-----
LU | Lung				
LUAVCRIZR	First-Line Treatment of ROS1-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib	*Eligibility updated*	-----	-----
LUAVPMBM	Maintenance Therapy of Advanced Non-Small Cell Lung Cancer with Pembrolizumab	*Eligibility clarified*	-----	-----
LUAVPMBM6	Maintenance Therapy of Advanced Non-Small Cell Lung Cancer with 6-Weekly Pembrolizumab	*Eligibility clarified*	-----	-----
LUAVPPMBM	Maintenance Therapy of Advanced Non-Squamous Non-Small Cell Lung Cancer with Pemetrexed and Pembrolizumab	*Eligibility clarified*	-----	-----
LY | Lymphoma				
LYCODOXMR	Treatment of Burkitt's Lymphoma and Leukemia (ALL-L3) with Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Leucovorin (CODOX-M) and Rituximab	*Eligibility and Exclusions clarified; 2nd IT lab and treatment added; note for holding anticoagulation added; HBV DNA monitoring clarified*	*2nd IT lab and treatment added; note for anticoagulation management added*	-----
LYHDMRTEM	Treatment of Primary and Secondary CNS Lymphoma with High-Dose Methotrexate, Rituximab and Temozolomide	*Eligibility and Exclusions clarified; prorated MTX dosing clarified; HBV DNA monitoring clarified*	-----	-----

REVISED Protocols, PPPOs and Patient Handouts *(revisions in respective columns)*				
Protocol Code	**Protocol Title**	**Protocol**	**PPPO**	**Handout**
LYIT	Treatment of Lymphoma using Intrathecal Methotrexate and Cytarabine	*Weekly option added; treatment duration clarified; note for holding anticoagulation added*	*Weekly option added; Return Appointment Orders and labs revised; note for anticoagulation management added*	-----
LYIVACR	Treatment of Burkitt's Lymphoma and Leukemia (ALL-L3) with Ifosfamide, Mesna, Etoposide, Cytarabine (IVAC) and Rituximab	*Eligibility clarified; note for holding anticoagulation added; HBV DNA monitoring clarified*	*Note for anticoagulation management added*	-----
LYMECHLOR	Topical Mechlorethamine in Cutaneous T-Cell Lymphoma	*Eligibility updated*	-----	-----
LYOBBEND	Treatment of Rituximab-Refractory Follicular Lymphoma (FL) with Obinutuzumab in Combination with Bendamustine	*Hypersensitivity management clarified*	-----	-----
LYOBCHLOR	Treatment of Previously-Untreated Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma with Obinutuzumab and Chlorambucil	*Hypersensitivity management clarified*	-----	-----
LYVENOB	Treatment of Previously-Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using Venetoclax and Obinutuzumab	*Hypersensitivity management clarified*	-----	-----
LYVIPDRT	Treatment of Newly-Diagnosed Nasal, Extranodal Natural Killer (NK) or T-Cell lymphoma, using Concurrent Radiation and Weekly Cisplatin Followed by Etoposide, Ifosfamide, Cisplatin and Dexamethasone	*PO mesna added*	*Dose modifications added; PO mesna added*	-----
MY | Myeloma				
MYBORMTN	Maintenance Therapy of Multiple Myeloma using Bortezomib for Patients with the High-Risk Chromosome Abnormality	*Dose reduction for cyclophosphamide revised*	-----	-----
SC | Supportive Care				
SCNAUSEA	Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults	*Olanzapine dosing updated; scopolamine patch removed*	-----	-----

Resources and Contact Information

Resource	Phone	Email / Toll Free / Fax
Systemic Therapy Update: www.bccancer.bc.ca/health-professionals/clinical-resources/systemic-therapy/systemic-therapy-update		
Systemic Therapy Update Editor	604-877-6000 x 672649	bulletin@bccancer.bc.ca
Oncology Drug Information Cancer Drug Manual Editor Pharmacy Oncology Certification Nurse Educators	604-877-6275 250-519-5500 x 693742 250-712-3900 x 686820 604-877-6000 x 672638	druginfo@bccancer.bc.ca nbadry@bccancer.bc.ca rxchemocert@bccancer.bc.ca nursinged@bccancer.bc.ca
CAP – Compassionate Access Program	604-877-6277	cap_bcca@bccancer.bc.ca fax 604-708-2026
OSCAR – Online System for Cancer Drugs Adjudication and Reimbursement	888-355-0355	oscar@bccancer.bc.ca fax 604-708-2051
Manufacturer Patient Assistance Programs: http://www.bccancer.bc.ca/mpap		
Library/Cancer Information	604-675-8003	requests@bccancer.bc.ca toll free 888-675-8001 x 8003
Library Document Delivery	604-675-8002	requests@bccancer.bc.ca
Pharmacy Professional Practice Professional Practice, Nursing Provincial Systemic Therapy Program	604-877-6000 x 672247 604-877-6000 x 672623 604-877-6000 x 672247	mlin@bccancer.bc.ca BCCancerPPNAdmin@ehcnet.phsa.ca mlin@bccancer.bc.ca
BC Cancer – Abbotsford BC Cancer – Kelowna BC Cancer – Prince George BC Cancer – Surrey BC Cancer – Vancouver BC Cancer – Victoria	604-851-4710 250-712-3900 250-645-7300 604-930-2098 604-877-6000 250-519-5500	toll free 877-547-3777 toll free 888-563-7773 toll free 855-775-7300 toll free 800-523-2885 toll free 800-663-3333 toll free 800-670-3322
Community Oncology Network (CON) sites: To update your contact information, please contact: bulletin@bccancer.bc.ca		

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