Systemic Therapy Update

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

Inside This Issue:

EDITOR'S CHOICE

NEW PROGRAMS

The Provincial Systemic Therapy Program has approved the following programs effective 01 March 2014:

Genitourinary:

Axitinib for Metastatic Renal Cell Carcinoma (UGUAXIT) – Axitinib is an oral tyrosine kinase inhibitor (TKI) newly approved for patients with metastatic renal cell carcinoma (mRCC) with clear cell component after prior first-line TKI therapy with sunitinib (UGUSUNI), sorafenib (UGUSORAF), or pazopanib (UGUPAZO). Patients are eligible to receive either everolimus (UGUEVER) or axitinib (UGUAXIT) in this setting, but not the sequential use of these agents except for patients who have intolerance or contraindications to everolimus. Approval of this program was based on the AXIS trial, a phase III, open-label study comparing axitinib and sorafenib in 723 patients with mRCC who had prior systemic therapies (54% sunitinib). Axitinib was associated with improved median progression-free survival (PFS) (6.7 mo vs. 4.7 mo, HR 0.66 [95% CI 0.54-0.81]), but no significant difference in overall survival (OS) or quality of life. The results were similar in the pre-specified subgroup of patients who had received prior sunitinib. [Motzer et al. Lancet 2013;14:552–62] More details about this drug can be found in the Cancer Drug Manual section of the current Systemic Therapy Update issue.

EDITOR'S CHOICE

Leukemia:

Peginterferon Alfa-2a Therapy for Chronic Myeloid Neoplasms and Hypereosinophilic Syndrome (LKPEGIFN) – Peginterferon alfa-2a (PEGASYS®) is now approved for patients with chronic myeloid neoplasms if they are intolerant or refractory to hydroxyurea. Chronic myeloid neoplasms consist of various myeloproliferative neoplasms, including:

- polycythemia vera
- myelofibrosis
- essential thrombocythemia
- systemic mastocytosis

Peginterferon is also indicated for patients with eosinophilic disorders refractory to steroids or hydroxyurea, including:

- idiopathic hypereosinophilic syndrome
- chronic eosinophilic leukemia NOS
- lymphocyte-variant hypereosinophilia

Peginterferon has been shown to have disease modifying activity in these patient populations but with a better toxicity profile than regular interferon. [Kiladjian et al. Blood 2008;112:3065-72, Gotlib. Am J Hematol 2011;86:678-88, Pardanani A. Blood 2013;121:3085-94.]

Lung:

Crizotinib for Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) (ULUAVCRIZ) – Crizotinib, an oral small molecule inhibitor of the ALK receptor tyrosine kinase and its oncogenic variants, is now approved as second-line therapy after one prior chemotherapy regimen containing a platinum. [Shaw et al. NEJM 2013;368:2385-2394] Approval of this program was based on the PROFILE 1007 trial, a phase III randomized, open-label study comparing crizotinib versus standard chemotherapy (containing pemetrexed or docetaxel) in 347 patients with previously treated ALK-positive, advanced NSCLC. Crizotinib was associated with superior median PFS (7.7 mo vs. 3.0 mo, HR 0.49 [95% CI 0.37-0.64]), higher response rate (65% vs. 20%, p<0.001), but no difference in median OS at the interim analysis (20.3 mo vs. 22.8 mo, HR 1.02 [95% CI 0.68-1.54]. [Shaw et al. NEJM 2013;368:2385-2394] Overall rates of adverse effects were higher in the crizotinib than the chemotherapy arm. Common toxicities included vision disturbances, diarrhea, nausea, vomiting, constipation, elevated aminotransferase levels, dizziness and edema.

About 5% of all NSCLC are ALK-positive. Therefore, patients must be tested and confirmed for ALK-positive advanced NSCLC prior to treatment. Crizotinib is administered orally at 250 mg twice daily. Because crizotinib is both a substrate and an inhibitor of CYP 3A4, the concurrent use of strong CYP 3A4 inhibitors (e.g. grapefruit juice) may significantly increase crizotinib toxicity while strong CYP3A4 inducers may reduce the effectiveness of crizotinib. Patients should be counselled to exercise caution while driving if they experience any visual disturbances (e.g. diplopia, blurred vision, etc.) as these were reported in 60% of patients in the PROFILE 1007 study.

HIGHLIGHTS OF CHANGES IN PROTOCOLS, PPPOS AND PATIENT HANDOUTS

Management of Elevated INR in Patients Treated with Bevacizumab-Based Protocols and PPPOs:

All BCCA chemotherapy protocols containing bevacizumab have been revised to indicate that

EDITOR'S CHOICE

bevacizumab should be held if the INR is greater than 3.0. This warning has been added under the Precautions section for "thrombosis" in the protocols and pre-printed orders.

Patients over 65 years of age or with a history of arterial thromboembolic events (ATE) are at increased risk of ATE during treatment with bevacizumab. Conversely, there is an increased risk of hemorrhage associated with giving bevacizumab to patients with elevated INR on warfarin therapy. Therefore, affected BCCA protocols have been revised to hold a bevacizumab dose when the INR is above 3.0. This change does not affect the required laboratory tests for bevacizumab-based protocols because regular INR monitoring is already mandatory for patients receiving warfarin therapy.

Brand Name Added in Trastuzumab-Based Protocols and PPPOs:

HERCEPTIN, the brand name for trastuzumab, has been added to the protocol title and treatment sections of all BCCA protocols containing trastuzumab. This change follows the recent Health Canada alert regarding the potential risk for mix-up between trastuzumab (HERCEPTIN) and trastuzumab emtansine (KADCYLA, also known as T-DM1). Note that the registered trademark symbol of "®" is not added after the brand name to limit the use of symbols in medication orders. Trastuzumab emtansine (KADCYLA) is currently not a BCCA benefit drug.

COMMUNITIES ONCOLOGY NETWORK

REMINDER: OSCAR SUBMISSION DEADLINE 09 APRIL 2014

The 2013/14 fiscal year will end on Monday, 31 March 2014. This brings with it tight deadlines which must be met for external reporting to the Ministry of Health and the Office of the Comptroller General. To meet these deadlines, all claims for drug reimbursement for the fiscal year must be invoiced by 11:59 pm on Wednesday, 09 April 2014 via OSCAR (Online System for Cancer drugs Adjudication and Reimbursement). Any claims invoiced after that date will not be eligible for reimbursement. For more information, please contact oscar@bccancer.bc.ca.

CONTINUING PROFESSIONAL DEVELOPMENT

CONFERENCES

MASCC/ISOO International Symposium on Supportive Care in Cancer 2014

Date: June 26-28, 2014
Location: Miami, FL
Early Bird Registration Deadline: 01 May 2014
Website: www.mascc.org/mascc-symposia

The Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO) jointly present the 2014 International Symposium on Supportive Care in Cancer. The

Continuing Professional Development

focus of this multidisciplinary symposium is on new developments, challenges and modern technology in supportive cancer care, and will include topics of regional and global importance, particularly to the Central and South America and the Asia-Pacific regions.

Cancer Drug Manual

New Monographs and Patient Handouts

Axitinib Monograph and **Patient Handout** have been developed with expert review provided by Dr. Christian Kollmannsberger (Medical Oncologist, BCCA Genitourinary Tumour Group).

Axitinib is a second generation oral tyrosine kinase inhibitor which selectively inhibits the vascular endothelial growth factor (VEGF) receptors. The absorption of axitinib is reduced with increased gastric pH so it should not be taken at the same time as antacids. Grapefruit and grapefruit juice should be avoided while on axitinib due to potential CYP 3A4/5 inhibition, which can increase the toxicity of axitinib. Common side effects include anemia, diarrhea, nausea, fatigue and palmar-plantar erythrodysesthesia. Hypertension, including hypertensive crisis, has been reported, with a median onset within the first month of treatment. Reversible posterior leukoencephalopathy syndrome (RPLS) and hemorrhagic events have also been reported. As impaired wound healing is associated with VEGFR-inhibitors, axitinib should be stopped 24 hours prior to surgery. It may be resumed post-surgery based on the clinical assessment of the wound healing.

Arsenic Trioxide Monograph and **Patient Handout** have been developed with expert review provided by Dr. Sujaatha Narayanan of the Leukemia/Bone Marrow Transplant Program of BC. Arsenic trioxide is an inorganic form of arsenic with a multi-modal mechanism of action, including partial cellular differentiation and DNA fragmentation leading to apoptosis and inhibition of angiogenesis of tumour cells. It is indicated for the induction of remission and as consolidation therapy in acute promyelocytic leukemia (APL). Highlights of the monograph and handout include:

- Arsenic can cause increased heart rate, QT prolongation, and complete AV block. QT prolongation tends to develop during the first three to four weeks of treatment; assessment of patients with cardiac risk factors and correction of electrolytes is required prior to treatment.
- Renal impairment may result in overdose levels of arsenic.
- APL differentiation syndrome is reported in about 30% of patients treated with arsenic trioxide; it is observed most often during induction and may be more common in patients with hyperleukocytosis. Symptoms include dyspnea, unexplained fever or hypotension, weight gain, acute renal failure, peripheral edema, acute congestive heart failure, interstitial pulmonary infiltrates, and pleuropericardial effusion.

Please note that arsenic trioxide is currently not a BCCA benefit drug.

Cancer Drug Manual

Deleted Monographs and Patient Handouts

The following Monographs and Patient Handouts have been deleted as the drugs are no longer commercially available in Canada (more details can be found in the February issue of the Systemic Therapy Update):

- Ibritumumab monograph
- Tositumumab monograph

Cancer Drug Manual Membership

The Cancer Drug Manual Writing Team and Editorial Board would like to welcome new team member Dr. Carrie Kung, Provincial Drug Information Specialist, and new board member Dr. Deepa Wadhwa, Medical Oncologist, Sindi Ahluwalia Hawkins Centre for the Southern Interior. Welcome!

Benefit Drug List

New Programs

The following programs have been added to the Benefit Drug List effective 01 March 2014:

Protocol Title	Protocol Code	Benefit Status
Therapy for Metastatic Renal Cell Carcinoma Using Axitinib	UGUAXIT	Restricted
Peginterferon Alfa-2a Therapy of Chronic Myeloid Neoplasms and Hypereosinophilic Syndrome	LKPEGIFN	Class II
Second-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib	ULUAVCRIZ	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 treatments requiring "Compassionate Access Program" (previously Undesignated Indications Request) approval are prefixed with the letter "U".

NEW Protocols, PPPOs and Patient Handouts (affected documents are checked):

CODE	Protocol	PPPO	Patient Handout	Protocol Title

NEW PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):				
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Protocol Title**
UGUAXIT	☑	☑	☐	Therapy for Metastatic Renal Cell Carcinoma Using Axitinib
LKPEGIFN	☑	☑	☐	Peginterferon Alfa-2a Therapy of Chronic Myeloid Neoplasms and Hypereosinophilic Syndrome
ULUAVCRIZ	☑	☑	☐	Second-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
BRAJACTW	☑	☑	☐	*Lab work clarified, Dose Modification for weekly paclitaxel added to PPPO, Return Appointment clarified in PPPO*	Adjuvant Therapy for Early Breast Cancer using DOXOrubicin and Cyclophosphamide followed by Weekly PACLitaxel
BRAJDCARBT	☑	☑	☐	*Brand name for trastuzumab added*	Adjuvant Therapy for Breast Cancer Using DOCEtaxel, CARBOplatin, and Trastuzumab (HERCEPTIN)
BRAJTR	☑	☑	☐	*Brand name for trastuzumab added, lower case for drug names formatted*	Adjuvant Therapy for Breast Cancer using Trastuzumab (HERCEPTIN) Following the Completion of Chemotherapy (Sequential)
UBRAVPTRAD	☑	☑	☐	*Brand name for trastuzumab added, lower case for drug names formatted*	Palliative Therapy for Metastatic Breast Cancer Using Pertuzumab, Trastuzumab (HERCEPTIN), and DOCEtaxel as First-Line Treatment for Advanced Breast Cancer
UBRAVTCAP	☑	☑	☐	*Brand name for trastuzumab added, lower case for drug names formatted*	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab and Capecitabine
BRAVTPCARB	☑	☑	☐	*Brand name for trastuzumab added, brand name for paclitaxel deleted*	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN), PACLitaxel and CARBOplatin as First-Line Treatment for Advanced Breast Cancer
BRAVTR	☑	☑	☐	*Brand name for trastuzumab added, lower case for drug names formatted*	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab
BRAVTRAD	☑	☑	☐	*Brand name for trastuzumab added, lower case for drug names formatted*	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN) and DOCEtaxel as First-Line Treatment for Advanced Breast Cancer

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
BRAVTRAP	☑	☑	☐	*Brand name for trastuzumab added, lower case for drug names formatted*	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN) and PACLitaxel as First-Line Treatment for Advanced Breast Cancer
BRAVTRVIN	☑	☑	☐	*Brand name for trastuzumab added, lower case for drug names formatted*	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN) and Vinorelbine
GIAVTZCAP	☐	☑	☐	*Temozolomide administration clarified*	Palliative Therapy of Metastatic Neuroendocrine Cancer Using Temozolomide and Capecitabine
GICIRB	☑	☑	☐	*Management of elevated INR added*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Bevacizumab and Capecitabine
UGICOXB	☑	☑	☐	*Management of elevated INR added*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Bevacizumab and Capecitabine
GIFFIRB	☑	☑	☐	*Management of elevated INR added, lower case for drug names formatted*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Bevacizumab and Capecitabine
UGIFFOXB	☑	☐	☐	*Management of elevated INR added, lower case for drug names formatted*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Leucovorin, and Bevacizumab
GIGAJCPRT	☑	☑	☐	*Tests clarified, TALLman lettering for drug names formatted*	Adjuvant Chemotherapy of Gastric Cancer Patients with Completely Resected Gastric Cancer using CISplatin and Capecitabine and Radiation Therapy
GIGAVCCT	☑	☑	☐	*Brand name for trastuzumab added*	Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma using CISplatin, Capecitabine and Trastuzumab (HERCEPTIN)
GIGAVCFT	☑	☑	☐	*Brand name for trastuzumab added*	Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma using CISplatin, Infusional Fluorouracil and Trastuzumab (HERCEPTIN)
GUBEP	☑	☐	☐	*Eligibility clarified, lower case for drug names formatted*	Curative Therapy for Germ Cell Cancer using with Bleomycin, Etoposide, CISplatin for Germ Cell Cancers

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
UGUPAZO	☑	☐	☐	*Minor typo corrected*	Palliative Therapy for Renal Cell Carcinoma Using Pazopanib
UGUSORAF	☑	☑	☐	*TALLman lettering for drug names formatted*	Palliative Therapy for Renal Cell Carcinoma Using SORAfenib
UGUSUNI	☑	☑	☐	*Minor typo corrected, TALLman lettering for drug names formatted*	Palliative Therapy for Renal Cell Carcinoma Using SUNItinib
HNAVPD	☑	☐	☐	*Sequence of chemotherapy administration clarified*	Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck with Platinum and DOCEtaxel
HNNAVPG	☐	☐	☑	*Carboplatin option added*	Treatment of Locoregionally recurrent or Metastatic Nasopharyngeal Cancer with Platinum and Gemcitabine
HNSAVPAC	☐	☑	☐	*Electrolyte concentration in hydration fluid clarified*	Treatment of Advanced Salivary Gland Cancers with Platinum, DOXOrubicin, and Cyclophosphamide
ULKMFRUX	☑	☐	☐	*Eligibility clarified*	Treatment of Symptomatic Myelofibrosis with Ruxolitinib
SAVAC	☑	☐	☐	*Emetogenicity revised, vincristine infusion duration clarified*	Adjuvant Therapy for Newly Diagnosed Ewing's Sarcoma/Peripheral Neuroectodermal Tumour (PNET) or Rhabdomyosarcoma Using vinCRIStine, DOXOrubicin and Cyclophosphamide
SAVACM	☑	☐	☐	*TALLman lettering formatted, vinCRIStine infusion and hydration duration clarified*	Adjuvant Therapy for Newly Diagnosed Ewing's Sarcoma/Peripheral Neuroectodermal Tumour (PNET) or Rhabdomyosarcoma with Pelvic Primaries or Chemotherapy Induced Hematuria Using vinCRIStine, DOXOrubicin, Cyclophosphamide and Mesna
SAVDCM	☑	☐	☐	*Emetogenicity revised, vincristine infusion and hydration duration clarified, optional hydration added*	Adjuvant Therapy for Rhabdomyosarcoma Using vinCRIStine, Dactinomycin, Cyclophosphamide and Mesna

Website Resources and Contact Information

Website Resources	www.bccancer.bc.ca
Systemic Therapy Update	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/stupdate
Reimbursement & Forms: Benefit Drug List, Class II, Compassionate Access Program	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Forms
Cancer Drug Manual	www.bccancer.bc.ca/cdm
Cancer Management Guidelines	www.bccancer.bc.ca/CaMgmtGuidelines
Cancer Chemotherapy Protocols, Pre-printed Orders, Protocol Patient Handouts	www.bccancer.bc.ca/ChemoProtocols
Systemic Therapy Program Policies	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Policies
CON Pharmacy Educators	http://www.bccancer.bc.ca/HPI/Pharmacy/ContactUs.htm

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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		
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Editorial Review Board