

Systemic Therapy Update

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For Health Professionals Who Care For Cancer Patients

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EDITOR'S CHOICE

New Programs

Effective 01 February 2019, the BC Cancer Provincial Systemic Therapy Program has approved the following treatment programs:

Multiple Myeloma:

Daratumumab in Combination with Bortezomib/Dexamethasone (UMYDARBD) or Lenalidomide/ Dexamethasone (UMYDARLD) for Multiple Myeloma – The Provincial Systemic Therapy Program has approved daratumumab in combination with either bortezomib/dexamethasone (Bor-dex) or lenalidomide/dexamethasone (Len-dex) for multiple myeloma after failure of at least 1 line of prior therapy. Patients must be sensitive to bortezomib to be eligible for UMYDARBD and sensitive to lenalidomide to be eligible for UMYDARLD. Full details for eligibility are outlined in the protocols.

Daratumumab is a human IgGk monoclonal antibody that targets CD38 which is highly expressed on myeloma cells. In a Phase III randomized controlled trial (CASTOR), the addition of daratumumab to Bor-dex improved progression free survival (mPFS not yet reached vs. 7.2 mo, HR 0.39 [95% CI 0.28 to 0.53]) and complete response rates (19.2% vs. 9.0%, p=0.001).¹ Final survival analysis is pending. The addition of oral cyclophosphamide will be permitted based on evidence presented in a single-arm Phase II trial (LYRA).²

EDITOR'S CHOICE

These results were similarly shown in a separate Phase III randomized controlled trial (POLLUX), where the addition of daratumumab to Len-dex showed a reduction in the risk of disease progression or death (18.5% vs. 41%, HR 0.37 [95% CI 0.27 to 0.52]) and an improved complete response rate (43.1% vs. 19.2%, p<0.001).³

Daratumumab is associated with tolerable, but not insignificant, adverse effects. In particular, about 50% of patients treated with daratumumab experienced infusion-related reactions. ¹ A majority (98%) of these reactions occurred with the first infusion, and primarily during or within the first 4 hours of infusion. As such, strict guidelines for premedication (with dexamethasone, acetaminophen, diphenhydramine and montelukast), daratumumab administration rate, and patient observation (during and after infusion) are clearly outlined in the chemotherapy protocols.

Daratumumab also follows a complicated dosing regimen that differs from cycle to cycle; dosing instructions on the chemotherapy protocols should be carefully observed. Of note, there are two administration options for the first daratumumab dose in cycle 1 (i.e. cycle 1 day 1):

- Standard regimen give daratumumab over 1 day
- Alternative regimen give daratumumab over 2 days (to accommodate the shorter operational hours of most ambulatory cancer clinics)

Gastrointestinal:

Oxaliplatin in Combination with Trastuzumab and 5-Fluorouracil (GIGAVFFOXT) or Capecitabine (GIGAVCOXT) for HER2-Positive Advanced Gastric, Gastroesophageal Junction or Esophageal Adenocarcinoma – The 2010 landmark ToGA trial established cisplatin, 5-fluorouracial/capecitabine and trastuzumab (GIGAVCCT, GIGAVCFT) as the standard of care for these GI malignacies.⁴ Since then, cisplatin has been largely replaced by oxaliplatin due to improved tolerability. In a retrospective study, trastuzumab with FOLFOX resulted in a median overall survival of 17 months and a median progression free survival of 9 months. These results did not appear to be numerically inferior to the clinical benefit seen in the ToGA trial.⁵ Trastuzumab with FOLFOX was also more convenient to administer and had acceptable tolerability.

The BC Cancer Gastrointestinal Tumour Group has now formalized the oxaliplatin-based regimens as the preferred standard of care in this patient population. Patients currently on the cisplatin-based regimens may remain on these regimens or switch to the oxaliplatin-based regimens without the need to apply for BC Cancer Compassionate Access Program (CAP) approval.

References:

- Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375:754-766.
- Yimer HA, Melear J, Faber E, et al. Lyra: A Phase 2 Study of daratumumab (dara), plus cyclophosphamide, bortezomib and dexamethasone in newly diagnosed and relapsed patients (Pts) with Multiple Myeloma (MM). Oral and poster abstract presented at: 60th ASH Annual Meeting; 2018 Dec 1; San Diego, CA.
- Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375:1319-1331.
- Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376;9742:687-697.
- Soularue É, Cohen R, Tournigand C, et al. Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastro-oesophageal junction adenocarcinoma patients: a retrospective study. Bull Cancer 2015;102:324-331.

PROVINCIAL SYSTEMIC THERAPY PROGRAM POLICIES

DARATUMUMAB ADDED TO PSTP POLICY III-60

Daratumumab has been added to the Provincial Systemic Therapy <u>Policy III-60</u> – Drug Reaction Management – Physician Coverage During Delivery of Selected Systemic Therapy Drugs.

DRUG UPDATE

ORAL ETOPOSIDE CAPSULES AVAILABLE

Etoposide *oral capsules* are once again available in Canada. Stock is now available in BC, but supplies will be on allocation by the manufacturer, Bristol Myers-Squibb, to ensure they continue to be available across Canada.

MEDICAL PATIENT ASSISTANCE PROGRAMS

The BC Cancer Medical Staff Engagement Society (MSES) generously provided financial support to organize a comprehensive, up-to-date listing of oncology medical patient assistance programs offered by pharmaceutical companies. The listing can be found at: www.bccancer.bc.ca/mpap.* Future updates to such provisional bridging programs will be announced periodically in the Systemic Therapy Update.

*Located on the BC Cancer Systemic Therapy website under Health Professionals > Systemic Therapy > Reimbursement & Forms

BENEFIT DRUG LIST

New Programs

Effective 01 February 2019, the following treatment programs have been added to the BC Cancer <u>Benefit</u> <u>Drug List</u>:

Protocol Title	Protocol Code	Benefit Status
Palliative Treatment of Metastatic or Locally Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma using Capecitabine, Oxaliplatin and Trastuzumab (HERCEPTIN)	GIGAVCOXT	Class I
Palliative Treatment of Metastatic or Locally Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma Using Oxaliplatin, Fluorouracil, Leucovorin, and Trastuzumab (HERCEPTIN)	GIGAVFFOXT	Class I
Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Bortezomib and Dexamethasone with or without Cyclophosphamide	UMYDARBD	Restricted
Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Lenalidomide and Dexamethasone	UMYDARLD	Restricted

BENEFIT DRUG LIST

REVISED PROGRAMS

Effective 01 February 2019, the following treatment programs have been revised on the BC Cancer <u>Benefit</u> <u>Drug List</u>:

Protocol Title	Protocol Code	Benefit Status
Therapy for Advanced Renal Cancer using Temsirolimus	GUTEM	Class I
Second-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib	LUAVCRIZ	Class I
First-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib	LUAVCRIZF	Class I

CANCER DRUG MANUAL

New Monographs and Patient Handouts

The following drug is <u>NOT</u> a BC Cancer Benefit Drug and requires application to the BC Cancer Compassionate Access Program (CAP). Its corresponding Interim Monograph and Patient Handout are made available for reference only. All BC Cancer drug monographs and patient handouts can be accessed on the BC Cancer <u>Drug Index</u>.

The **Inotuzumab ozogamicin Interim Monograph and Patient Handout** have been developed with expert review provided by Dr. David Sanford (hematologist) of the BC Cancer Leukemia and Bone Marrow Transplant Tumour Group. Inotuzumab ozogamicin is an antibody-drug conjugate composed of a humanized monoclonal antibody (inotuzumab) linked to a small molecule cytotoxic agent (N-acetyl-gamma-calicheamicin). Inotuzumab ozogamicin is used as monotherapy in adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia. The usual dose for cycle 1 is 0.8 mg/m² on day 1 and 0.5 mg/m² on days 8 and 15, given intravenously. Cycle 2 and optional additional cycles are dosed based on whether a complete response was achieved in cycle 1, and are given every 3 to 4 weeks.

Highlights of these documents:

- Premedication with a corticosteroid, antihistamine, and antipyretic is recommended for all patients prior to each dose to prevent infusion-related reactions
- Myelosuppression and infections are commonly reported
- Severe, and sometimes, fatal veno-occlusive disease/sinusoidal obstruction syndrome has been reported; monitor for elevated bilirubin, hepatomegaly, rapid weight gain and ascites
- Other rare, but serious, side effects include tumour lysis syndrome and QT-prolongation

CANCER DRUG MANUAL

REVISED MONOGRAPHS AND PATIENT HANDOUTS

Highlights of key changes and/or updates to the Monographs, Patient Handouts and Chemotherapy Preparation and Stability Chart (CPSC) are listed below:

Carfilzomib Monograph

Cautions, Special Populations, and Side Effects: updated incidence and risk factors for cardiac failure

Clodronate Patient Handout

Revised statements on indications and drug interactions

Daratumumab Monograph, Patient Handout and CPSC

Dosing: added BC Cancer protocol and standard dosing

Pamidronate Patient Handout and CPSC

- Added adjuvant indications and expanded on drug interactions
- CPSC: added Pfizer as new brand

Pembrolizumab Monograph

- Uses: updated Health Canada approved indications
- Dosing: added fixed-dose regimens and updated pediatric dosing

Zoledronic Acid Patient Handout

Added adjuvant indications and expanded on drug interactions

LIST OF REVISED PROTOCOLS, PRE-PRINTED ORDERS 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. Protocol codes for treatment requiring BC Cancer Compassionate Access Program approval are prefixed with the letter "U".

New Protocols, PPPOs and Patient Handouts (Affected Documents are Checked)					
CODE	Protocol	РРРО	Patient Handout	Protocol Title	
GIGAVCOXT	V	V	V	Palliative Treatment of Metastatic or Locally Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma using Capecitabine, Oxaliplatin and Trastuzumab (HERCEPTIN)	
GIGAVFFOXT	V	V	V	Palliative Treatment of Metastatic or Locally Advanced Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma using Oxaliplatin, Fluorouracil, Leucovorin, and Trastuzumab (HERCEPTIN)	
UMYDARBD	V	V		Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Bortezomib and Dexamethasone with or without Cyclophosphamide	

New Protocols, PPPOs and Patient Handouts (Affected Documents are Checked)					
CODE Protocol PPPO Patient Handout Protocol Title					
UMYDARLD	V	V		Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Lenalidomide and Dexamethasone	

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)						
CODE	Protocol	РРРО	Patient Handout	Changes	Protocol Title	
CNCCNU	V	\checkmark		Reformatted, test updated	Lomustine (CCNU) for Treatment of Recurrent Malignant Brain Tumours	
CNETO	V	\checkmark		Reformatted, test updated	Palliative Treatment of Patients with Recurrent Malignant Gliomas and Ependymoma using Low Dose Etoposide	
CNPROC	Ø	\checkmark		Reformatted, test updated	Standard Procarbazine for Second-Line Treatment of Recurrent Brain Tumour	
CNTEM60	V	\checkmark		Reformatted, test updated	Therapy for Newly Diagnosed Malignant Brain Tumours with MGMT Methylation in Elderly Patients using Temozolomide	
CNTEMOZ	V	\checkmark		Reformatted, test updated	Therapy for Malignant Brain Tumours using Temozolomide	
CNTEMOZMD	V	\checkmark		Reformatted, test updated	Therapy for Malignant Brain Tumours using Metronomic Dosing of Temozolomide	
CNTMZETO	V	V		Reformatted, test updated	Therapy for Recurrent Malignant Brain Tumours using Temozolomide and Etoposide	
GIGAVTR	V			Eligibility updated	Continuation of Palliative Treatment of Metastatic or Inoperable, Locally Advanced Gastric or Gastroesophageal Junction Adenocarcinoma using Trastuzumab	
UGILAN	V		V	Duration of approved treatment updated	Symptomatic Management of Functional Carcinoid and Neuroendocrine Tumours of the GI Tract using Lanreotide (SOMATULINE AUTOGEL)	
UGIOCTLAR	V	\checkmark	V	Duration of approved treatment updated	Symptomatic Management of Functional Carcinoid and Neuroendocrine Tumors of the GI Tract using Octreotide (SANDOSTATIN LAR)	
GUTEM	V	\checkmark	V	Eligibility updated	Therapy for Advanced Renal Cancer using Temsirolimus	
ULKMFRUX	V	\checkmark		Duration of approved treatment updated	Treatment of Symptomatic Myelofibrosis with Ruxolitinib	
ULKPCVRUX	V	\checkmark		Duration of approved treatment updated	Treatment of Polycythemia Vera with Ruxolitinib	

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)						
CODE	Protocol	РРРО	Patient Handout	Changes	Protocol Title	
LUAVCRIZ	V	V	V	Eligibility updated	Second-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib	
ULUAVPMTN	\checkmark	\checkmark	V	Duration of approved treatment updated	Maintenance Therapy of Advanced Non-Small Cell Lung Cancer (NSCLC) with Pemetrexed	
SAVDC	Ø	V		Treatment options, Contact Physician and institution name updated	Adjuvant Therapy for Rhabdomyosarcoma using Vincristine, Dactinomycin, and Cyclophosphamide	

The following BC Cancer Pre-Printed Orders (PPPOs) have been reformatted:

CODE	Protocol Title
BRAJANAS	Neoadjuvant or Adjuvant Therapy for Breast Cancer using Anastrozole in Postmenopausal Women
BRAJEXE	Neoadjuvant or Adjuvant Therapy for Breast Cancer using Exemestane in Postmenopausal Women
BRAJLET	Neoadjuvant or Adjuvant Therapy for Breast Cancer using Letrozole in Postmenopausal Women
BRAJLHRHT	Neoadjuvant or Adjuvant Therapy for Breast Cancer using a LHRH Agonist and Tamoxifen
BRAJTAM	Neoadjuvant or Adjuvant Therapy for Breast Cancer using Tamoxifen
BRAVANAS	Palliative Therapy for Metastatic Breast Cancer using Anastrozole
BRAVCLOD	For Therapy of Bone Metastases in Breast Cancer using Oral Clodronate
BRAVEXE	Palliative Therapy for Advanced Breast Cancer using Exemestane
BRAVLET	Palliative Therapy for Advanced Breast Cancer using Letrozole
BRAVMEG	Palliative Therapy for Advanced Breast Cancer using Megestrol
BRAVTAM	Palliative Therapy for Breast Cancer using Tamoxifen
CNAJ12TZRT	Concomitant (Dual Modality) and 12 Cycles of Adjuvant Temozolomide for Newly Diagnosed Astrocytomas and Oligodendrogliomas with Radiation
CNAJTZRT	Concomitant (Dual Modality) and Adjuvant Temozolomide for Newly Diagnosed Malignant Gliomas with Radiation
CNB	Therapy for Pituitary Adenomas using Bromocriptine
CNCAB	Therapy for Pituitary Adenomas using Cabergoline
CNELTZRT	Treatment of Elderly Newly Diagnosed Glioma Patient with Concurrent and Adjuvant Temozolomide and Radiation Therapy
CNQUIN	Therapy for Pituitary Adenomas using Quinagolide

CODE	Protocol Title
GIAJCAP	Adjuvant Therapy of Colon Cancer using Capecitabine
GIAVCAP	Palliative Therapy of Advanced Colorectal Cancer using Capecitabine
GIPAVCAP	Second-Line Treatment of Metastatic or Unresectable Pancreatic Adenocarcinoma using Capecitabine
GUPNSAA	Non-Steroidal Treatment of Prostate Cancer
HNNAVCAP	Treatment of Recurrent Or Metastatic Nasopharyngeal Cancer with Capecitabine
HNSAVTAM	Treatment of Recurrent/Metastatic Salivary Gland Cancers of the Head and Neck with Tamoxifen
LUAVAFAT	First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Afatinib
ULUAVCER	Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Ceritinib
LUAVCRIZ	Second-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib
LUAVCRIZF	First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Afatinib
LUAVERL	Second- or Later-Line Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with Erlotinib
LUAVGEFF	First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Gefitinib
LUAVMTNE	Maintenance Therapy of Advanced Non-Small Cell Lung Cancer (NSCLC) with Erlotinib After First-Line Chemotherapy
LUSCPOE	Palliative Therapy of Extensive Stage Small Cell Lung Cancer (SCLC) with Oral Etoposide
LYCHLOR	Therapy for Low Grade Lymphoma and Chronic Lymphocytic Leukemia using Chlorambucil
LYCSPA	Cyclosporine for Cytopenias Associated with Lymphoproliferative Disorder of Large Granular Lymphocytes
ULYMFBEX	Treatment for Refractory Cutaneous T-cell Lymphoma using Bexarotene
МҮМР	Treatment of Multiple Myeloma using Melphalan and Prednisone

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