BC CANCER
Provincial Health Services Authority

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 September 2018, the BC Cancer Provincial Systemic Therapy Program has approved the following treatment programs:

Gynecologic:

Carboplatin with Pegylated Liposomal Doxorubicin (CAELYX®) for First-Line Treatment of Epithelial Ovarian Cancer (**GOOVFPLDC**) – The standard systemic therapy for patients with invasive epithelial ovarian cancer is carboplatin with paclitaxel (GOOVCATM, GOOVCATX, GOOVDDCAT). Patients who are not suitable for paclitaxel therapy may be treated with carboplatin with docetaxel (GOOVCAD). The Provincial Systemic Therapy Program has now approved carboplatin with CAELYX® (GOOVFPLDC) as another treatment alternative in this setting. In a phase III randomized controlled trial (MITO-2), carboplatin plus CAELYX® demonstrated similar overall survival, progression free survival, and quality of life when compared to carboplatin plus paclitaxel in the first-line treatment of advanced ovarian cancer.[1]

Olaparib Maintenance Therapy in Relapsed, BRCA-Mutated, Platinum-Sensitive and Responsive Epithelial Ovarian Cancer (UGOOVOLAPM) – The BC Cancer Gynecologic Oncology Tumour Group is introducing this new treatment program in patients who have completed at least two lines of platinum-based therapy and demonstrated radiologic response to the most recent line of platinum-based therapy. Olaparib shall be started within 8 weeks of the last dose of platinum-based therapy. In a phase III randomized placebo-controlled trial (SOLO II), olaparib was associated with improved progression-free survival (median PFS 19.1 mo vs. 5.5 mo, HR 0.30 95% CI 0.22-0.41).[2] The most common serious adverse events included anemia, fatigue, asthenia and neutropenia.

EDITOR'S CHOICE

Medication Error Caution: Olaparib is commercially available in tablets and capsules which are NOT interchangeable (different dosing and bioavailability). BC Cancer is funding olaparib TABLETS only. Patients who are currently on olaparib capsules shall be switched to the tablet formulation as per recommended dosing on the UGOOVOLAPM treatment protocol.

Lung:

Ceritinib for ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) (ULUAVCER) – The BC Cancer Lung Tumour Group is introducing this new treatment for ALK-positive advanced NSCLC that has progressed following crizotinib therapy. In a phase III randomized controlled trial (ASCEND-5), ceritinib was associated with improved progression free survival compared to chemotherapy (median PFS 5.4 mo vs. 1.6 mo, HR 0.49 95% CI 0.36-0.67). [3] The most common serious adverse event associated with ceritinib was elevated hepatic enzymes.

References:

1. Pignata S, et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. J Clin Oncol 2011;29(27):3628-35.
2. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2*mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274-1284.
3. Shaw AT, Kim TM, Crino L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017;18(7):874-886.

DRUG UPDATE

DRUG SHORTAGE: ETOPOSIDE ORAL CAPSULES

There is an etoposide oral capsule shortage in Canada. The only Canadian supplier, Bristol-Myers Squibb, estimates that this will be a long-term backorder, with an anticipated return supply date of six months or longer. Across both BC Cancer and the Communities Oncology Network, the current supply is estimated to be sufficient until around mid-September.

It is recommended that no NEW patients start etoposide oral capsules at this time. Please consider use of the following recommended alternative protocols where appropriate:

Tumour Group	Etoposide Capsule-Containing Protocols	Alternative Protocols
CNS	CNBEV	CNCCNU
	CNETO	CNCCNU
	CNTMZETO	Contact Tumour Group
GYNE	GOOVETO	GOOVVIN, GOOVTAX3, GOOVLDOX, GOOVGEM, GOOVCYCPO, GOOVETO (IV option)
	GOSMCCRT	Cisplatin 25 mg/m^2/day IV x 3 days and etoposide 100 mg/m^2/day IV daily for 3 days every 3 weeks (as per LUSCPE)
LU	LUSCPOE	Single-agent etoposide 100 mg/m^2/day IV daily for 3 days every 3 weeks
LY	LYCHOP LYCHOPR	Etoposide 50 mg/m^2/day IV daily for 3 days (instead of 1 day of IV etoposide plus 2 days of oral etoposide)
	LYPALL	LYPALL (IV option)

Drug Update

Another option is to administer the etoposide IV solution orally as the IV solution and capsule formulations have similar bioavailability when ingested orally. The following outlines the recommended steps in preparing etoposide IV solution for oral administration.

- Dilute etoposide injection with bacteriostatic sodium chloride 0.9% injection to a concentration of 10 mg/mL
- Store the prepared solution in oral syringes or in amber glass bottles
- Prepared solution is stable for 22 days at room temperature
- Shake well before use
- Prepared solution can be further diluted immediately prior to administration in apple juice, orange juice or lemonade (NOT grapefruit juice). To enhance taste, concentration should be less than 0.4 mg/mL. For example, dilute 50 mg (5 mL) oral solution to at least 125 mL with fruit juice. More concentrated solutions in fruit juice may result in precipitation in less than 3 hours.

References:
1. Aguilar Ponce JL, Flores-Picazo Y, Perez-Urizar J, et al. Bioavailability after oral administration of the solution marketed for intravenous use: therapeutic and pharmacoeconomic perspectives. Archives of Medical Research 1999; 30(3): 212-5.
2. Lam MSH. Extemporaneous compounding of oral liquid dosage formulations and alternative drug delivery methods for anticancer drugs. Pharmacotherapy 2011; 31(2):164-192.
3. McLeod HL, Relling MV. Stability of etoposide solution for oral use. American Journal of Hospital Pharmacists 1992;49(November):2784-2785.

Benefit Drug List

New Programs

Effective 01 September 2018, the following treatment programs have been added to the BC Cancer Benefit Drug List:

Protocol Title	Protocol Code	Benefit Status
Primary Treatment with Visible or No Visible Residual Tumour (Moderate, High, or Extreme Risk) or Treatment at Relapse of Invasive Epithelial Ovarian, Fallopian Tube, and Primary Peritoneal Cancer, using Carboplatin and Docetaxel (Replaces GOOVCADM, GOOVCADR, GOOVCADX)	GOOVCAD	Class I
First-Line Treatment of Epithelial Ovarian Cancer using Doxorubicin Pegylated Liposomal (CAELYX™) and Carboplatin	GOOVFPLDC	Class I
Maintenance Treatment of Relapsed, BRCA-mutated, Platinum-Sensitive and Responsive Epithelial Ovarian Cancer using Olaparib	UGOOVOLAPM	Restricted
Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Ceritinib	ULUAVCER	Restricted

BENEFIT DRUG LIST

DELETED PROGRAMS

Effective 01 September 2018, the following treatment programs have been deleted from the BC Cancer Benefit Drug List.

Protocol Title	Protocol Code
Primary Treatment of Invasive Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer, with No Visible Residual Tumour (Moderate-High Risk) using Carboplatin and Docetaxel	GOOVCADM (replaced by GOOVCAD)
Second-Line Treatment using Docetaxel and Carboplatin for Epithelial Ovarian Cancer Relapsing After Primary Treatment	GOOVCADR (replaced by GOOVCAD)
Primary Treatment of Visible Residual (Extreme Risk) Invasive Epithelial Ovarian Cancer using Carboplatin and Docetaxel	GOOVCADX (replaced by GOOVCAD)

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NEW MONOGRAPHS AND PATIENT HANDOUTS

The following drugs are NOT BC Cancer Benefit Drugs, and require application to the BC Cancer Compassionate Access Program. Their corresponding Interim Monographs are made available for reference only.

Belinostat Interim Monograph has been developed and added to the **Chemotherapy Preparation and Stability Chart**. Belinostat is a histone deacetylase (HDAC) inhibitor. By inhibiting the enzymatic activity of HDAC, belinostat causes the accumulation of acetylated histones and other proteins, thus inducing cell cycle arrest and/or apoptosis of transformed cells. Belinostat shows preferential cytotoxicity towards tumour cells and exhibits its activity at nanomolar concentrations. The recommended dosing is 1000 mg/m^2 IV once daily for 5 days, in a 21-day cycle. The starting dose should be reduced in patients homozygous for the UGT1A1*28 allele. The most commonly reported serious adverse reactions are pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia and multi-organ failure. Tumour lysis syndrome has also been reported in patients with advanced stage disease and/or high tumour burden; appropriate prophylaxis is recommended. Please note that belinostat is not commercially available in Canada and requires access through the Health Canada Special Access Programme (SAP).

Durvalumab Interim Monograph has been developed and added to the **Chemotherapy Preparation and Stability Chart**. Durvalumab is a humanized IgG1 monoclonal antibody immune checkpoint inhibitor that binds to programmed death-ligand 1 (PD-L1) and blocks the interaction with PD-1 and B7-1 receptors on T-lymphocytes. Blocking these receptors restores anti-tumor T-cell activity. The recommended dosing is 10 mg/kg IV once every two weeks. Overall, durvalumab appears to be well tolerated with the majority of adverse reactions being grades 1 and 2 in severity. Most are reversible with treatment interruption or administration of steroids. The most common adverse events are diarrhea, pneumonitis, rash, pruritus,

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fatigue and decreased appetite. Pneumonia, pneumonitis, back pain, urinary tract infection, acute kidney injury, elevated liver function tests and general health deterioration most commonly led to dose interruption or delay. Infusion-related reactions are uncommon (2%) but severe reactions are possible. Similar to other immune checkpoint inhibitors, durvalumab is associated with immune-mediated adverse events such as endocrinopathies, diarrhea/colitis, hepatitis, nephritis, pneumonitis and rash. Immune-mediated reactions should be managed according to their severity; treatment interruption and/or corticosteroids may be indicated.

Revised Monographs and Patient Handouts

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

Lenalidomide Monograph:

- *Cautions:* added statement about possibility of solid organ transplant rejection
- *Side Effects table:* added solid organ transplant rejection and graft-versus-host disease
- *Supply and Storage:* updated available capsule strengths

Olaparib Monograph and **Patient Handout:**

- Information on new tablet formulation, new controlled distribution program for capsule formulation, and cautionary statement that *tablets* and *capsules* are NOT interchangeable have been added to multiple sections
- *Interactions:* revised recommendations for olaparib dose reduction during concurrent therapy with itraconazole and CYP 3A inhibitors
- *Dosing:* added standard dosing of tablet formulation, updated information on capsule formulation, revised dosing in renal failure
- *Patient Handout:* changed "capsule" to "tablet", added information on availability of multiple tablet strengths
- *Auxiliary Label chart:* added tablet formulation, updated recommendation to administer capsules on an empty stomach

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	PPPO	Patient Handout	Protocol Title
GOOVCAD	☑	☑	☐	Primary Treatment with Visible or No Visible Residual Tumour (Moderate, High, or Extreme Risk) or Treatment at Relapse of Invasive Epithelial Ovarian, Fallopian Tube, and Primary Peritoneal Cancer, using Carboplatin and Docetaxel (replaces GOOVCADM, GOOVCADR, GOOVCADX)

NEW PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)				
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Protocol Title**
GOOVFPLDC	☑	☑	☐	First-Line Treatment of Epithelial Ovarian Cancer using Doxorubicin Pegylated Liposomal (CAELYX®) and Carboplatin
UGOOVOLAPM	☑	☑	☐	Maintenance Treatment of Relapsed, BRCA-mutated, Platinum-Sensitive and Responsive Epithelial Ovarian Cancer Using Olaparib
ULUAVCER	☑	☑	☑	Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Ceritinib

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
BRAVGEMP	☐	☐	☑	*Minor typo corrected*	Palliative Therapy for Metastatic Breast Cancer using Cisplatin and Gemcitabine
GOCXCATB	☐	☑	☐	*Tests clarified*	Treatment of Metastatic or Recurrent Cancer of the Cervix with Bevacizumab, Carboplatin and Paclitaxel
UGOOVBEVG	☑	☐	☐	*Eligibility clarified*	Treatment of Platinum-Resistant Epithelial Ovarian Cancer with Bevacizumab and Gemcitabine
UGOOVBEVLD	☑	☐	☐	*Eligibility clarified*	Treatment of Platinum-Resistant Epithelial Ovarian Cancer with Bevacizumab and Doxorubicin Pegylated Liposomal (CAELYX®)
UGOOVBEVP	☑	☐	☐	*Eligibility clarified*	Platinum-Resistant Epithelial Ovarian Cancer with Bevacizumab and Paclitaxel
UGOOVBEVV	☑	☐	☐	*Eligibility clarified*	Treatment of Platinum-Resistant Epithelial Ovarian Cancer with Bevacizumab and Vinorelbine
GOOVCARB	☐	☑	☐	*Return Appointment section revised*	First- or Second-Line Therapy for Invasive Epithelial Ovarian Cancer using Single-Agent Carboplatin
GOOVCATM	☐	☑	☐	*Return Appointment section revised*	Primary Treatment of No Visible Residual (Moderate-High Risk) Invasive Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer using Carboplatin and Paclitaxel
GOOVCATX	☐	☑	☐	*Return Appointment section revised*	Primary Treatment of Visible Residual (Extreme Risk) Invasive Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer using Carboplatin and Paclitaxel
GOOVCYCPO	☑	☐	☐	*Title corrected, Eligibility clarified*	Palliative Therapy for Relapsed/Progressing Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Metronomic Low-Dose Oral Cyclophosphamide

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
GOOVDDCAT	☐	☑	☐	*Return Appointment section revised*	Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Carboplatin and Weekly Paclitaxel
GOOVDOC	☑	☑	☐	*Eligibility and dilution bag clarified*	Treatment of Relapsed/Progressing Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Docetaxel
GOOVETO	☑	☐	☐	*Eligibility clarified*	Treatment of Relapsed/Progressing Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Etoposide
GOOVGEM	☑	☐	☐	*Eligibility clarified*	Treatment of Relapsed/Progressing Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Gemcitabine
GOOVIPPC	☐	☑	☐	*Return Appointment section revised*	Primary Treatment of Stage III Less Than or Equal to 1 cm Visible Residual Invasive Epithelial Ovarian Cancer or Stage I Grade 3 or Stage II Grade 3 Papillary Serous Ovarian Cancer using Intravenous and Intraperitoneal Paclitaxel and Intraperitoneal Carboplatin
GOOVLDOX	☑	☐	☐	*Eligibility clarified*	Treatment of Epithelial Ovarian Cancer Relapsing after Primary Treatment using Doxorubicin Pegylated Liposomal (CAELYX®)
GOOVPLDC	☑	☐	☐	*Preface and Dosing calculation clarified*	Treatment of Epithelial Ovarian Cancer Relapsing after Primary Treatment using Doxorubicin Pegylated Liposomal (CAELYX®) and Carboplatin
GOOVTAX3	☑	☐	☐	*Eligibility clarified*	Treatment of Relapsed/Progressing Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Paclitaxel
GOOVTOP	☑	☐	☐	*Eligibility clarified*	Treatment of Relapsed/Progressing Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Topotecan
GOOVVIN	☑	☐	☐	*Eligibility clarified*	Treatment of Relapsed/Progressing Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma using Vinorelbine
GUAJPG	☑	☐	☐	*Eligibility clarified*	Adjuvant Therapy for Urothelial Carcinoma using Cisplatin and Gemcitabine
ULKMDSA	☑	☐	☐	*Treatment duration clarified*	Therapy of Myelodysplastic Syndrome using Azacitidine
ULUAVCRIZ	☑	☑	☑	*Tests clarified, institutional name updated*	Second-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Crizotinib
LUAVDC	☐	☐	☑	*Institutional name and logo updated*	Treatment of Advanced Non-Small Cell Lung Cancer with Cisplatin and Docetaxel

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
LUAVDOC	☐	☐	☑	*Institutional name and logo updated*	Second- or Later-Line Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with Docetaxel
ULUAVPMTN	☐	☐	☑	*Institutional name and logo updated*	Maintenance Therapy of Advanced Non-Small Cell Lung Cancer (NSCLC) with Pemetrexed
LUAVNP	☐	☐	☑	*Institutional name and logo updated*	Treatment of Advanced Non-Small Cell Lung Cancer with Cisplatin and Vinorelbine
LUAVNP (Carboplatin)	☐	☐	☑	*Institutional name and logo updated*	Treatment of Advanced Non-Small Cell Lung Cancer with Carboplatin and Vinorelbine
LUAVPEM	☐	☐	☑	*Institutional name updated*	Second-Line Chemotherapy of Advanced Non-Small Cell Lung Cancer (NSCLC) with Pemetrexed
LUAVPG	☐	☐	☑	*Institutional name and logo updated*	Treatment of Advanced Non-Small Cell Lung Cancer with Cisplatin and Gemcitabine
LUAVPG (Carboplatin)	☐	☐	☑	*Institutional name and logo updated*	Treatment of Advanced Non-Small Cell Lung Cancer with Carboplatin and Gemcitabine
LUAVVIN	☐	☐	☑	*Institutional name and logo updated*	Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with Vinorelbine
LYEPOCHR	☑	☐	☐	*Rituximab dosing schedule clarified*	Treatment of Lymphoma with Dose-Adjusted Etoposide, Doxorubicin, Vincristine, Cyclophosphamide, Prednisone and Rituximab with Intrathecal Methotrexate
USMAVPEM	☑	☑	☐	*Dosing clarified*	Treatment of Unresectable or Metastatic Melanoma using Pembrolizumab

DELETED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)				
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Protocol Title**
GOOVCADM	☑	☑	☐	Primary Treatment of Invasive Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer, with No Visible Residual Tumour (Moderate-High Risk) using Carboplatin and Docetaxel (replaced by GOOVCAD)
GOOVCADR	☑	☑	☐	Second-Line Treatment using Docetaxel and Carboplatin for Epithelial Ovarian Cancer Relapsing After Primary Treatment (replaced by GOOVCAD)
GOOVCADX	☑	☑	☐	Primary Treatment of Visible Residual (Extreme Risk) Invasive Epithelial Ovarian Cancer using Carboplatin and Docetaxel (replaced by GOOVCAD)

Website Resources and Contact Information

Contact Information	Phone	Fax	Email
Systemic Therapy Update Editor	604-877-6000 x 673028		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
Nurse Educators	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
Provincial Professional Practice Nursing			BCCancerPPNAdmin@ehcnet.phsa.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 Oncology Certification	250-712-3900 x 686820		rxchemocert@bccancer.bc.ca
BC Cancer-Abbotsford	604-851-4710 Toll Free 877-547-3777		
BC Cancer-Prince George (Centre for the North)	250-645-7300 Toll Free 888-775-7300		
BC Cancer-Surrey	604-930-2098 Toll Free 800-523-2885		
BC Cancer-Kelowna	250-712-3900 Toll Free 888-563-7773		
BC Cancer-Vancouver	604-877-6000 Toll Free 800-663-3333		
BC Cancer-Victoria	250-519-5500 Toll Free 800-670-3322		

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