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

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

Genitourinary

Neoadjuvant Dose-Dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin for Urothelial Cancer (GUBDDMVAC) — The BC Cancer Genitourinary Tumour Group is implementing a treatment alternative for patients with clinically suspected or pathologically determined T2-T4 urothelial cancer and no evidence of metastatic disease. Methotrexate, vinblastine, doxorubicin and cisplatin (ddMVAC) are administered in 14-day cycles with filgrastim support, prior to definitive treatment (surgery or chemoradiation). Until now, the standard of care for muscle-invasive urothelial cancer has been platinum-based neoadjuvant chemotherapy, largely based on extrapolation of metastatic data. GUBDDMVAC is an alternative to neoadjuvant platinum-gemcitabine (GUNAJPG).

Approval for this treatment program is supported by the randomized, controlled phase III VESPER trial comparing perioperative ddMVAC to platinum-gemcitabine; most patients received chemotherapy prior to surgery.[1,2] Improvement in progression-free survival was seen in the subgroup of patients who received neoadjuvant ddMVAC (HR 0.70, 95% CI 0.51-0.96). In addition, immature data show a strong trend towards improved overall survival in this subgroup (HR 0.66, 95% CI 0.47-0.92). Grade 3 or greater anemia (22% vs.

7.8%), febrile neutropenia (6.5% vs. 2.4%), asthenia (14% vs. 4.1%) and nausea/vomiting (9.7% vs. 2.9%) were observed more frequently in the ddMVAC group.

Lung

Ipilimumab and 3-Weekly Nivolumab for Malignant Mesothelioma (LUMMIPNI3) — The BC Cancer Lung Tumour Group is adding a 3-weekly nivolumab option to the ipilimumab-nivolumab combination treatment for patients with previously untreated unresectable malignant mesothelioma.[3,4] The original ipilimumab-nivolumab combination treatment (LUMMIPNI) was introduced 01 May 2022 using 2-weekly nivolumab – please see corresponding issue of the Systemic Therapy Update. Both treatment protocols deliver ipilimumab every 6 weeks. CAP approval is not required to switch between LUMMIPNI and LUMMIPNI3. Patients who were started on first-line platinum doublet therapy prior to 01 May 2022, and are still receiving it, may switch to LUMMIPNI3 or LUMMIPNI if they have not experienced progression and meet other eligibility criteria.

- **LUMMIPNI:**

Drug	Dosage	Schedule
ipilimumab	1 mg/kg	every 6 weeks
nivolumab	3 mg/kg *(maximum 240 mg)*	every 2 weeks

- **LUMMIPNI3:** *(new)*

Drug	Dosage	Schedule
ipilimumab	1 mg/kg	every 6 weeks
nivolumab	4.5 mg/kg *(maximum 360 mg)*	every 3 weeks

References

1 Pfister C, Gravis G, Flechon A, et al. Randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin, or gemcitabine and cisplatin as perioperative chemotherapy for patients with muscle-invasive bladder cancer. Analysis of the GETUG/AFU V05 VESPER trial secondary endpoints: chemotherapy toxicity and pathological responses. *Eur Urol* 2021;79(2):214-221. https://doi.org/10.1016/j.eururo.2020.08.024

2 Pfister C, Gravis G, Flechon A, et al. Abstract 652O – Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for patients with muscle-invasive bladder cancer (MIBC): Results of the GETUG/AFU VESPER V05 phase III trial. *Ann Oncol* 2021;32(suppl_5):S678-S724. https://doi.org/10.1016/annonc/annonc675

3 CADTH Reimbursement Recommendation. Nivolumab in combination with ipilimumab (Opdivo®-Yervoy®). *Canadian Journal of Health Technologies* 2021;1(8). https://www.cadth.ca/sites/default/files/pcodr/Reviews2021/PC0229%20Opdivo-Yervoy%20%20Final%20Rec.pdf

4 Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multi-centre, randomised, open-label, phase 3 trial. *Lancet* 2021;397(10272):375-386. https://doi.org/10.1016/S0140-6736(20)32714-8

DPYD Genotyping for Patients Experiencing Severe Toxicity with Fluorouracil or Capecitabine

Dihydropyrimidine Dehydrogenase (DPD) Enzyme Activity

Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency is an inherited disorder of pyrimidine metabolism.[1] Over 80% of fluorouracil and capecitabine, both fluoropyrimidine drugs, are metabolized and inactivated by the DPD enzyme.[1,2] Reduced DPD enzyme activity is associated with the accumulation of active metabolites, putting patients at increased risk of early, severe and life-threatening toxicities with standard doses of fluoropyrimidines.[3] As such, fluoropyrimidines are contraindicated in patients with complete or near-complete absence of DPD enzyme activity.[1,2]

DPYD Genotyping for Patients Experiencing Severe Toxicity with Fluorouracil or Capecitabine

DPYD Genotyping

The DPD enzyme is encoded by the *DPYD* gene.[3] *DPYD* genotyping can be used to identify genetic variants that can predict decreases in DPD enzyme activity. Patients with genetic variation in the *DPYD* gene are at risk of severe toxicities with fluoropyrimidines due to the impaired metabolizing ability of the DPD enzyme. There is increasing evidence that *DPYD* genotyping prior to fluoropyrimidine treatment is important for guiding starting dose recommendations. Four well-studied *DPYD* gene variants have a prevalence of 3-8% in the Western population; these same *DPYD* gene variants have an established link to fluoropyrimidine toxicity, providing strong support for *DPYD* genotype-guided dosing.[4] In 2020, the European Medicines Agency recommended that all patients being treated with fluoropyrimidines should be tested for DPD enzyme activity.[5] Clinical guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) recommend specific starting dose reductions for patients with an identified *DPYD* gene variant based on their predicted DPD enzyme activity.[4,6]

Research Study at BC Cancer – Vancouver

A pilot study at BC Cancer – Vancouver will be investigating the use of *DPYD* genotyping for patients initiating treatment with fluorouracil or capecitabine. Using a genotype-guided approach to dose individualization, this study aims to reduce fluoropyrimidine-induced morbidity and mortality. The study will also provide prospective evidence for genotyping six *DPYD* variants in a Canadian setting. For questions about the study, contact Angela Wu at awu@popi.ubc.ca.

On-Demand *DPYD* Testing

On-demand reactive testing for the six *DPYD* variants will be available to patients BC-wide using the Cancer Genetics and Genomics Laboratory requisition form (see below).

Requisition Form and Dosing Table

- A requisition form for *DPYD* genotyping will be viewable in Cerner, and can be downloaded from the Cancer Genetics and Genomics Laboratory
- A dosing table is available in the BC Cancer Drug Manual© Appendix and Drug Index

References

1 Fluorouracil Monograph. Revised 01 September 2021. In: BC Cancer Drug Manual©. Badry, Nadine (editor). BC Cancer. Vancouver, British Columbia. Available at http://www.bccancer.bc.ca/

2 Capecitabine Monograph. Revised 01 May 2021. In: BC Cancer Drug Manual©. Badry, Nadine (editor). BC Cancer. Vancouver, British Columbia. Available at http://www.bccancer.bc.ca/

3 Henricks LM, Lunenburg CATC, Meulendijks D, et al. Translating *DPYD* genotype into DPD phenotype: using the *DPYD* gene activity score. *Pharmacogenomics* 2015;16(11):1275-1284. https://doi.org/10.2217/pgs.15.70

4 Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. *Clin Pharmacol Ther* 2018;103(2):210-216. https://doi.org/10.1002/cpt.911

5 European Medicines Agency. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine. 2020. https://www.ema.europa.eu/en/documents/referral/fluorouracil-fluorouracil-related-substances-article-31-referral-new-testing-treatment_en.pdf

6 Lunenburg CATC, van der Wouden CH, Nijenhuis M, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of *DPYD* and fluoropyrimidines. *Eur J Human Gen* 2020;28:508–517. https://doi.org/10.1038/s41431-019-0540-0

Drug Update

Subcutaneous Daratumumab Coming Soon

Daratumumab for subcutaneous administration will become available for all daratumumab-containing protocols (UMYDARBD, UMYDARCBDF, UMYDARLD, UMYDARLDF) as of 01 September 2022. With the change from intravenous administration to subcutaneous administration, a 12-15% decrease in nurse time and a 50% decrease in patient chair time are expected over the first 8 months of treatment, with the majority of nurse and chair time improvements realized in the first three cycles of treatment. Treatment sites may notice an increase in the number of patients booked per day due to the reduced time requirement for subcutaneous daratumumab administration.

More information and education will be provided in late August, prior to the September ST Update.

Education Corner

Extravasation Hazard of Antibody-Drug Conjugates: Focus on Vedotins

An antineoplastic antibody-drug conjugate (ADC) combines a monoclonal antibody with a cytotoxic drug via a chemical linker. The antibody component is designed to bind to a target surface antigen that is unique or overexpressed on cancer cells. After binding to the target antigen on the surface of the cancer cell, the ADC is internalized by the cancer cell. The linker is then cleaved enzymatically, releasing the cytotoxic drug component inside the cancer cell. Theoretically, in the event of a tissue extravasation, the cytotoxic drug should not present as a significant extravasation hazard, unless there is a significant number of normal cells expressing the target antigen, or there are cancer cells present in the area of extravasation.

Brentuximab vedotin and polatuzumab vedotin are ADCs containing monomethylauristatin E (MMAE), an antimitotic cytotoxic drug component.[1,2] When released intracellularly, MMAE causes disruption of microtubules, cell cycle arrest and apoptosis. Based on new data, these drugs have been reclassified as irritants in the event of a tissue extravasation, with the potential for vesicant-like properties. One patient was reported to develop reversible erythema, blisters and demyelinating neuropathy after extravasation of brentuximab vedotin; no tissue necrosis or ulceration was described.[3] Given that there were no cancer lesions in the area of extravasation, it is unclear how MMAE could have been released and caused the adverse effects. Although there are no reported cases with polatuzumab vedotin, it has also been reclassified because it has the same cytotoxic drug component, MMAE. If an extravasation occurs with either drug, the infusion should be stopped and the patient monitored for reactions.

See Systemic Therapy **Policy III-20: Prevention and Management of Extravasation of Chemotherapy** on SHOP and the **BC Cancer Extravasation Hazard Table** in the BC Cancer Drug Manual© Appendix.

References

1 Brentuximab Vedotin Monograph. Revised 01 August 2022. In: BC Cancer Drug Manual©. Badry, Nadine (editor). BC Cancer. Vancouver, British Columbia. Available at http://www.bccancer.bc.ca/.

2 Polatuzumab Vedotin Monograph. Revised 01 August 2022. In: BC Cancer Drug Manual©. Badry, Nadine (editor). BC Cancer. Vancouver, British Columbia. Available at http://www.bccancer.bc.ca/.

3 Hoffmann JC, Soliman M, Koch JC, et al. Demyelinating neuropathy and local toxicity caused by extravasated brentuximab vedotin. *J Eur Acad Derm Venereol* 2020;34:e626-e628. https://doi.org/10.1111/jdv.16502

Medication Safety

Safety of Pets When Administering Cancer Drugs at Home

Institute for Safe Medication Practices (ISMP) has to date issued two alerts regarding the inadvertent exposure of pets to fluorouracil, resulting in toxicity and potential fatality to the pets. In one incident, the pet died after chewing the tubing of an intravenous fluorouracil preparation delivered at home.[1] Veterinarians have also reported high mortality rates in pets who have licked the skin of patients who had applied topical fluorouracil.[2] In response to an analysis of these incidents, the BC Cancer Medication Safety Subcommittee reviewed the BC Cancer patient education handouts for intravenous and topical cancer drugs. *"Your Infusor – A Guide for Patients"* – a handout for patients receiving fluorouracil continuous infusion at home via elastomeric infusor – includes a caution about pets, however, no analogous language was present in patient education materials for topical drugs. A caution has now been added to the Cancer Drug Manual patient handouts for topical fluorouracil, imiquimod and chlormethine, to bring awareness to patients such that they can minimize unintentional exposure of topical cancer drugs to their pets.

References

1 Institute for Safe Medication Practices (ISMP). More on fluorouracil and pets. ISMP Medication Safety Alert! Acute Care. 2021;26(18):3.

2 Institute for Safe Medication Practices (ISMP). Keep topical fluorouracil far away from pets. ISMP Medication Safety Alert! Acute Care. 2020;25(24):4.

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 a 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 **Tucatinib Interim Monograph** and **Patient Handout** have been developed with expert review provided by Dr. Stephen Chia (medical oncologist) and Khushminder Rai (clinical pharmacist) of the BC Cancer Breast Tumour Group. Tucatinib is an orally administered HER2-selective tyrosine kinase inhibitor. Tucatinib is used in combination with trastuzumab and capecitabine in the treatment of breast cancer. The usual dose is 300 mg twice daily.

Highlights from these documents include:

- diarrhea is frequently reported (median time to onset 12 days); severe events associated with dehydration, acute renal failure and death, have occurred
- dose modification of tucatinib may be required for drug interactions involving CYP 2C8 metabolism
- hepatotoxicity is common; liver function should be monitored regularly throughout treatment

Tucatinib has been added to the **Auxiliary Label List**, and has been evaluated for the **BC Health Authorities Provincial Hazardous Drug List**.

Cancer Drug Manual©

Revised Documents

Brentuximab Vedotin Monograph and **Patient Handout**
Side Effects: updated extravasation hazard to irritant
Patient Handout (*Side Effects* table): added template statement for vesicants/irritants; updated nausea/vomiting and diarrhea entries in *Side Effects* table with dehydration comment; updated peripheral neuropathy management

Chlormethine Topical Patient Handout
Bullets: added warning about close contact with children and pets

Fluorouracil Topical Patient Handout
Bullets: added warning about close contact with children and pets

Imiquimod Topical Patient Handout
Bullets: added warning about close contact with children and pets

Ipilimumab Monograph and **Patient Handout**
Uses: updated Health Canada-approved indications
Cautions: added statement about vaccination
Parenteral Administration table: updated infusion rate; added information about in-line filter
Dosage Guidelines: added new protocol dosing (LUAVPCIPNI and LUAVPPIPNI)
Dosage in renal failure: added dosing information for mild to moderate impairment
Dosage in hepatic failure: added dosing information for mild impairment
Patient Handout: added statement about vaccination in bullets

Nivolumab Monograph and **Patient Handout**
Uses: updated Health Canada-approved indications
Cautions: added statement about vaccination in bullets
Dosage Guidelines: added new protocol dosing (LUAVPCIPNI and LUAVPPIPNI)
Patient Handout: added statement about vaccination

Polatuzumab Vedotin Monograph and **Patient Handout**
Side Effects: updated extravasation hazard to irritant
Patient Handout (*Side Effects* table): added template statement for vesicants/irritants; updated nausea/vomiting and diarrhea entries in *Side Effects* table with dehydration comment; updated peripheral neuropathy management

Venetoclax Monograph and **Patient Handout**
Cautions: updated interactions bullet to differentiate recommendations in AML and CLL
Interactions: updated management of interactions for strong CYP 3A4 inhibitors
Dosage Guidelines: updated initiation and ramp-up schedule for CLL; added new initiation and ramp-up schedule for AML and new protocol dosing (ULKAMLAVEN); added warning about dose adjustment for drug interactions; updated dosing in hepatic failure
Patient Handout: updated interactions bullet; updated nausea/vomiting and diarrhea entries in *Side Effects* table with dehydration comment

Extravasation Hazard List
Brentuximab vedotin: upgraded to irritant, treat as vesicant
Polatuzumab vedotin: upgraded to irritant, treat as vesicant

BC Cancer Benefit Drug List

New Programs

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

Protocol Title	Protocol Code	Benefit Status
Neoadjuvant Treatment of Urothelial Cancer using Dose-Dense **Methotrexate**, **Vinblastine**, **Doxorubicin** and **Cisplatin**	**GUBDDMVAC**	Class I
Treatment of Malignant Mesothelioma using **Ipilimumab** and **3-Weekly Nivolumab**	**LUMMIPNI3**	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
GUBDDMVAC	Neoadjuvant Treatment of Urothelial Cancer using Dose-Dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin	☑	☑	☐
LUMMIPNI3	Treatment of Malignant Mesothelioma using Ipilimumab and 3-Weekly Nivolumab	☑	☑	☑

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

Protocol Code	Protocol Title	Protocol	PPPO	Handout
BR | Breast				
BRAJACTG	Neoadjuvant or Adjuvant Therapy for Breast Cancer using Dose-Dense Therapy: Doxorubicin and Cyclophosphamide Followed by Paclitaxel	*Eligibility clarified*	-----	-----
BRAJACTW	Neoadjuvant or Adjuvant Therapy for Early Breast Cancer using Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel	*Eligibility clarified*	-----	-----
BRAVLHRHAI	Therapy for Advanced Breast Cancer using a LHRH Agonist and an Aromatase Inhibitor	*Protocol code revised*	*Protocol code revised*	-----

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

Protocol Code	Protocol Title	Protocol	PPPO	Handout
LK | Leukemia				
LKGEMOZ	Treatment of Acute Myeloid Leukemia using Gemtuzumab Ozogamicin with Induction and Consolidation	*Supportive medications updated*	-----	-----
LU | Lung				
LUMMIPNI	Treatment of Malignant Mesothelioma using Ipilimumab and Nivolumab	*Eligibility updated*	-----	-----
LY | Lymphoma				
LYAVDBV	Treatment of Previously Untreated, Stage IV Hodgkin Lymphoma with Doxorubicin, Vinblastine, Dacarbazine and Brentuximab Vedotin	*Precautions updated*	-----	*Brentuximab vedotin extravasation caution added*
LYBRENTUX	Treatment of Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma with Brentuximab Vedotin	*Precautions updated*	-----	-----
LYBV	Consolidation Therapy Post-Autologous Stem Cell Transplant (ASCT) for Hodgkin Lymphoma using Brentuximab Vedotin	*Precautions updated*	-----	-----
LYCHPBV	Treatment of CD30-Positive Peripheral T-Cell Lymphoma (PTCL) with Doxorubicin, Cyclophosphamide, Prednisone (CHP) and Brentuximab Vedotin	*Precautions updated*	-----	*Brentuximab vedotin extravasation caution added*
LYCTCLBV	Treatment of Cutaneous T-Cell Lymphoma (CTCL) with Brentuximab Vedotin	*Precautions updated*	-----	-----
LYIVACR	Treatment of Burkitt Lymphoma and Leukemia (ALL-L3) with Ifosfamide, Mesna, Etoposide, Cytarabine (IVAC) and Rituximab	-----	*Supportive medications updated*	-----
LYPOLABR	Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Not-Eligible for Transplant using Polatuzumab Vedotin, Bendamustine and Rituximab	*Precautions updated*	-----	*Polatuzumab vedotin extravasation caution added*
LYVENOB	Treatment of Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using Venetoclax and Obinutuzumab	-----	*Tests clarified* **Cycle 1 PPPO**	-----

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	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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