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 program effective 1 May 2023. Full details of all treatment programs are available in the Chemotherapy Protocols section of the BC Cancer website.

### Gynecological

**Treatment of Cervical Cancer with Carboplatin, Paclitaxel, Pembrolizumab with or without Bevacizumab (UGOCXCATBP, UGOCXCATP, GOCXBP, GOCXBP6)** — The BC Cancer Gynecological Tumour Group is introducing the addition of pembrolizumab to chemotherapy with or without bevacizumab for patients with advanced cervical cancer. The phase III RCT, KEYNOTE- 826, demonstrated added clinical benefit of pembrolizumab to standard of care (SoC) regimens of chemotherapy for patients with PD-L1 (CPS $\geq$1) with medial OS of 18.3 months follow-up (hazard ratio [HR] = 0.64; 95% confidence interval [CI], 0.50 to 0.81; P value = 0.0001) compared to placebo. There was also statistically significant improvement in PFS (HR = 0.62; 95% CI, 0.50 to 0.77; P < 0.0001) compared to placebo. The treatment was associated with manageable toxicities consistent with the known safety profile of pembrolizumab.[1] BC Cancer Compassionate Access Program (CAP) approval is required for primary treatment protocols (UGOCXCATBP and UGOCXCATP).

**References**

1. Colombo N, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 2021;385(20):1856-67.

# Editor's Choice

## Fluorouracil and Capecitabine Dosing Based on DPYD Genotyping Activity Score

### Dihydropyrimidine Dehydrogenase (DPD) Enzyme Activity

Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency is an inherited disorder of pyrimidine metabolism. Over 80% of fluorouracil and capecitabine, both fluoropyrimidine drugs, are metabolized and inactivated by DPD.[1] Reduced DPD 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 fluorouracil and capecitabine.[1,2] As such, these agents are contraindicated in patients with complete or near-complete absence of DPD activity.[1,2] Note that trifluridine-tipiracil (LONSURF®) contains a fluoropyrimidine (trifluridine) that is metabolized by thymidine phosphorylase rather than DPD. Therefore, dosing of trifluridine-tipiracil is not affected by DPD deficiency.

### *DPYD* Genotyping

The DPD enzyme is encoded by the *DPYD* gene.[1,2] *DPYD* genotyping can help identify genetic variants to predict decreases in DPD activity. Patients with genetic variation in the *DPYD* gene can be at risk of severe toxicities with DPD-dependent fluoropyrimidines due to reduced metabolism of the active metabolites. Therefore, *DPYD* genotyping prior to fluorouracil or capecitabine treatment is important for guiding starting dose recommendations. Several *DPYD* gene variants have an established link to DPD-dependent fluoropyrimidine toxicity, providing strong support for *DPYD* genotype-guided dosing.[1,2] Therefore, all patients being treated with fluorouracil or capecitabine should be tested for DPD activity[3] and patients with an identified *DPYD* gene variant should start with reduced dose based on their predicted DPD activity.[1,2,4]

### Dosing of Fluorouracil and Capecitabine Guided by *DPYD* Activity Score

*DPYD* genotype is translated to phenotype through a predicted activity score.[2,4] This score is the sum of both alleles of a patient, and represents a patient's enzymatic phenotype. Non-functional alleles have an activity score of 0, reduced function alleles have an activity score of 0.5, and normal function alleles have an activity score of 1. For example, if a patient carries 1 reduced function allele, their activity score is 0.5 + 1 = 1.5. The dosing recommendations below are posted on the BC Cancer website: www.bccancer.bc.ca/cdm

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**Fluorouracil and Capecitabine Dosing Based on *DPYD* Activity Score (DPYD-AS)**

| Predicted Activity Score | Genotype | Likely *DPYD* Phenotype | Dosing for Fluorouracil and Capecitabine |
|---|---|---|---|
| 0 | Homozygous (or compound heterozygous) for a non-functional variant | Poor metabolizer | Do not use |
| 0.5 | One non-functional PLUS one reduced function variant | | Use not recommended<br>If no alternative option, reduce dose by at least 75% PLUS early therapeutic drug monitoring |
| 1.0 | Heterozygous for a non-functional variant | Intermediate metabolizer | Reduce dose by 50%.<br>Titrate future dose based on clinical judgement† |
| | Homozygous for a reduced function variant* | | |
| | Compound heterozygous for two reduced function variants | | |
| 1.5 | Heterozygous for a reduced function variant | | |
| 2.0 | Variant negative | Normal metabolizer | No dose reduction |

*Case reports from patients who are homozygous for c.2846A>T indicate that a dose reduction of more than 50% in the starting dose may be required in some carriers of this genotype. †Only consider escalating dose if no toxicity in cycle 1 and 2. Increase by a maximum of 10% per cycle

## DPYD Testing at BC Cancer

*DPYD* genotyping is now available for patients initiating treatment containing fluorouracil or capecitabine (prospective testing) and for patients who experienced severe toxicity from fluorouracil or capecitabine (retrospective testing). Note that testing is not indicated for patients successfully transiting through initial treatment cycles without an unanticipated adverse reaction.

## How to order a prospective DPYD test:

*DPYD* testing is performed weekly and the expected Turn Around Time (TAT) is routinely ≤ 10 calendar days. Actual TAT will depend on the day when the specimen is received at Cancer Genetics & Genomics Laboratory (CGL). If you anticipate that the patient is likely to be treated with fluorouracil or capecitabine, these can be ordered in advance of the patient being seen.

| CST-Cerner sites | Non-CST-Cerner sites |
|---|---|
| • Order the test through CERNER. Select "LAB-Miscellaneous Test (Blood)" in the search window → write "DPYD test" in the 'Name of the Lab test' field.<br>• Print the test requisition http://cancergeneticslab.ca/requisitions/ (select DPYD Genotyping) and give the patient the physical copy.* DO NOT FAX THIS TO THE CANCER GENETICS LAB – YOUR ORDER WILL GET CANCELLED. They can take the requisition to any biomedical laboratory.<br>• Test results will be received through the CERNER message center and updated on the patient's electronic record. | • Print the test requisition http://cancergeneticslab.ca/requisitions/ (select DPYD Genotyping) and give the patient the physical copy.* DO NOT FAX THIS TO THE CANCER GENETICS LAB – YOUR ORDER WILL GET CANCELLED. They can take the requisition to any biomedical laboratory.<br>• Physical copies of test results will be received through mail and test results will be posted in CAIS (and come into your action list). |

## How and where can patients have their blood drawn?

The patient can be given a physical copy of the requisition that can be taken to any phlebotomy lab For sample collection.

*Alternatively the completed requisition can be either e-mailed (a PDF copy) to LifeLabs at: PatientREQSBC@lifelabs.com or faxed to 1-888-674-0370. Note that the patients should be instructed to wait 24 hours after the requisition is submitted before going to any LifeLabs to ensure that the requisition has been processed.

## Other important information

Protocols, pre-printed orders and PowerPlan order sets will be updated over the next few months to reflect the availability of this test and dosing recommendations. However, initially the onus will be on the ordering clinician to ensure tests are ordered and results checked and actioned appropriately prior to prescribing the drug.

**References**


1 Wörmann B, Bokemeyer C, Burmeister T, et al. Dihydropyrimidine dehydrogenase testing prior to treatment with 5-fluorouracil, capecitabine, and tegafur: A Consensus Paper. Oncol Res Treat 2020;43(11):628-636.

2 Negarandeh R, Salehifar E, Saghafi F, et al. Evaluation of adverse effects of chemotherapy regimens of 5-fluoropyrimidines derivatives and their association with DPYD polymorphisms in colorectal cancer patients. BMC Cancer. 2020;20(1):560. Published 2020 Jun 16.

3 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.

4 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for diphydropyrimidine dehydrogenase genotype and fluropyrimidine dosing: November 2018 update. Available at: https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/

# Cancer Drug Manual©

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

## New Documents

The **Elranatamab Interim Monograph** has been developed. **Elranatamab** is a heterodimeric humanized (IgG2) bispecific antibody directed against B-cell maturation antigen (BCMA) and Cluster of differentiation 3 T-cell co-receptor (CD3). It is a T-cell directed therapy used in the treatment of multiple myeloma. Elranatamab is administered by subcutaneous injection in a 28 day cyclical regimen. Cycle 1 begins with two step-up priming doses (given on days 1 and 4), followed by the full dose administered on days 8, 15, and 22. For subsequent cycles, the full dose is administered on days 1, 8, 15, and 22. Outside of clinical trials, elranatamab is only available via the Health Canada Special Access Program.

Highlights from this document include:

- premedication is required for both priming doses and the first full dose (cycle 1 days 1, 4, and 8) to mitigate cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)
- closed system transfer devices (CSTDs) are acceptable to use for preparation, but they cannot be used for any period of storage of the prepared dose; prepared doses must be used immediately after preparation
- elranatamab is associated with impaired wound healing and bleeding which may be a risk following surgical procedures

**Elranatamab** has been added to the **Chemotherapy Preparation and Stability Chart** and has been evaluated for the **BC Health Authorities Provincial Hazardous Drug List.**

## Revised Documents

**Cytarabine Monograph**

*Cautions*: updated *Fertility* and *Pregnancy* sections
*Supply and Storage*: updated with current marketed brands
*Throughout*: updated all links

**Cytarabine Injection Patient Handout**

*Throughout:* updated template statements per current template
*Side Effects table:* added new information about eye/vision problems and revised confusion/memory loss to align with BC Cancer protocol handout LYDHAPR

**Chemotherapy Preparation and Stability Chart**

**DPACE**: added entry for 3-in-1 solution of etoposide, CISplatin, and cyclophosphamide for new protocol ULY0 D-PACE; cross referenced all brands of etoposide, CISplatin, and cyclophosphamide to DPACE
**Doxorubicin** (all brands): added entry for 1 litre bag for new protocol ULY0 D-PACE

# BC Cancer Benefit Drug List

## New Programs

The following treatment programs have been added to the Benefit Drug List effective 01 May 2023:

| Protocol Title | Protocol Code | Benefit Status |
|---|---|---|
| Maintenance Therapy of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with **Pembrolizumab** with or without **Bevacizumab** | GOCXBP | Class I |
| Maintenance Therapy of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with **6-Weekly Pembrolizumab** with or without **Bevacizumab** | GOCXBP6 | Class I |
| Primary Treatment of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with **Bevacizumab**, **CARBOplatin**, **PACLitaxel** and **Pembrolizumab** | UGOCXCATBP | Restricted |
| Primary Treatment of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with **CARBOplatin**, **PACLitaxel**, and **Pembrolizumab** | UGOCXCATP | Restricted |

## Revised Programs

The following treatment programs have been added to the Benefit Drug List effective 01 May 2023:

| Protocol Title | Protocol Code | Benefit Status |
|---|---|---|
| Treatment of Previously Untreated Multiple Myeloma and Not Eligible for Stem Cell Transplant Using Bortezomib, Lenalidomide and Dexamethasone | MYBLDF | Class I *(previously Restricted)* |
| Therapy of Multiple Myeloma Using Carfilzomib and Dexamethasone With or Without Cyclophosphamide | MYCARDEX | Class I *(previously Restricted)* |
| Therapy of Multiple Myeloma using Carfilzomib, Lenalidomide with Dexamethasone | MYCARLD | Class I *(previously Restricted)* |
| Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Bortezomib and Dexamethasone With or Without Cyclophosphamide | MYDARBD | Class I *(previously Restricted)* |
| Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Lenalidomide and Dexamethasone | MYDARLD | Class I *(previously Restricted)* |
| Therapy of Relapsed Multiple Myeloma Using Lenalidomide with Dexamethasone | MYLDREL | Class I *(previously Restricted)* |
| Maintenance Therapy of Multiple Myeloma Using Lenalidomide | MYLENMTN | Class I *(previously Restricted)* |

# 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 |
|---|---|---|---|---|
| **GOCXBP** | Maintenance Therapy of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with Pembrolizumab with or without Bevacizumab | ☑ | ☑ | ☑ |
| **GOCXBP6** | Maintenance Therapy of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with 6-Weekly Pembrolizumab with or without Bevacizumab | ☑ | ☑ | ☑ |
| **UGOCXCATBP** | Primary Treatment of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with Bevacizumab, CARBOplatin, PACLitaxel and Pembrolizumab | ☑ | ☑ | ☑ |
| **UGOCXCATP** | Primary Treatment of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with CARBOplatin, PACLitaxel, and Pembrolizumab | ☑ | ☑ | ☑ |
| **GUBDDMVAC** | Neoadjuvant Treatment of Urothelial Cancer using Dose-Dense Methotrexate, vinBLAStine, DOXOrubicin and CISplatin | -- | -- | ☑ |
| **LYDHAPR** | Treatment of Lymphoma with Dexamethasone, Cytarabine, Platinum and riTUXimab | -- | -- | ☑ |

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

| Protocol Code | Protocol Title | Protocol | PPPO | Handout |
|---|---|---|---|---|
| **GI \| Gstrointestinal** | | | | |
| **GIAVPANI** | Palliative Third Line Treatment of Metastatic Colorectal Cancer Using PANitumumab | *tests updated* | *tests updated* | -- |
| **GIAVPG** | First-line Palliative Chemotherapy for Advanced Gallbladder, Pancreatic Carcinoma, and Cholangiocarcinoma using Gemcitabine and CISplatin | *tests updated* | *tests updated* | -- |

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

| Protocol Code | Protocol Title | Protocol | PPPO | Handout |
|---|---|---|---|---|
| **GIFUC** | Palliative Chemotherapy for Upper Gastrointestinal Tract Cancer (Gastric, Esophageal, Gall Bladder, Pancreas Carcinoma and Cholangiocarcinoma) and Metastatic Anal using Infusional Fluorouracil and CISplatin | *treatment revised* | *treatment revised, maximum dose reformatted* | -- |
| **GIGAVTRFT** | Third- or Later-Line Therapy of Advanced Gastroesophageal Carcinoma Using Trifluridine-Tipiracil | -- | *maximum dose reformatted* | -- |
| **GIIR** | Palliative Chemotherapy of Metastatic Colorectal Cancer Using Irinotecan | -- | *maximum dose reformatted* | -- |
| **GO \| Gynecologic** | | | | |
| **GOCABR** | Alternative Treatment of Gynecological Malignancies using CARBOplatin and PACLitaxel NAB (ABRAXANE) | *eligibility, caution and tests updated* | -- | -- |
| **GOCABRBEV** | Alternative Treatment of Gynecological Malignancies using Bevacizumab, CARBOplatin and PACLitaxel NAB (ABRAXANE) | *eligibility, caution and tests updated* | -- | -- |
| **GOCISP** | Alternative Treatment of Gynecological Malignancies using CISplatin and PACLitaxel | *eligibility updated* | -- | -- |
| **GOCISPBEV** | Alternative Treatment of Gynecological Malignancies using Bevacizumab, CISplatin and PACLitaxel | *eligibility updated* | -- | -- |
| **GU \| Genitourinary** | | | | |
| **GUBDDMVAC** | Neoadjuvant Treatment of Urothelial Cancer using Dose-Dense Methotrexate, vinBLAStine, DOXOrubicin and CISplatin | -- | *prechemo metrics clarified* | -- |
| **GUMVAC** | Therapy for Transitional Cell Cancers of the Urothelium using Methotrexate, vinBLAStine, DOXOrubicin and CISplatin | -- | *prechemo metrics clarified* | -- |
| **LY \| Lymphoma** | | | | |
| **LYDARCBDF** | Treatment of Previously Untreated Light Chain Amyloidosis and Not Eligible for Stem Cell Transplant using Daratumumab, Cyclophosphamide, Bortezomib and Dexamethasone | -- | *maximum dose reformatted* | -- |
| **LYRITZ** | Palliative Therapy For Lymphoma Using Radioimmunotherapy: riTUXimab-Priming for 90Y-Ibritumomab Tiuxetan (ZEVALIN®) | *drug name clarified, contact physician updated* | -- | -- |
| **ULYROMI** | Treatment of Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL) with romiDEPsin | *new restriction added* | *new restriction added* | -- |
| **MY \| Myeloma** | | | | |

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

| Protocol Code | Protocol Title | Protocol | PPPO | Handout |
|---|---|---|---|---|
| **~~U~~MYBLDF** | Treatment of Previously Untreated Multiple Myeloma and Not Eligible for Stem Cell Transplant Using Bortezomib, Lenalidomide and Dexamethasone | *protocol code and contact physician updated, CAP requirement deleted* | *protocol code updated, CAP requirement deleted* | *protocol code updated* |
| **~~U~~MYCARDEX** | Therapy of Multiple Myeloma Using Carfilzomib and Dexamethasone With or Without Cyclophosphamide | *protocol code and contact physician updated, CAP deleted, exclusions updated* | *protocol code updated, CAP deleted* | *protocol code update* |
| **~~U~~MYCARLD** | Therapy of Multiple Myeloma using Carfilzomib, Lenalidomide with Dexamethasone | *protocol code, contact physician, CAP deleted* | *protocol code updated, CAP deleted* | *protocol code updated* |
| **~~U~~MYDARBD** | Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Bortezomib and Dexamethasone With or Without Cyclophosphamide | *protocol code and contact physician updated, CAP deleted* | *protocol code updated, CAP deleted* | *protocol code updated* |
| **~~U~~MYDARLD** | Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Lenalidomide and Dexamethasone | *protocol code and contact physician updated, CAP deleted* | *protocol code updated, CAP deleted* | *protocol code updated* |
| **~~U~~MYLDREL** | Therapy of Relapsed Multiple Myeloma Using Lenalidomide with Dexamethasone | *protocol code updated, CAP deleted* | *protocol code updated, CAP deleted* | *protocol code updated* |
| **~~U~~MYLENMTN** | Maintenance Therapy of Multiple Myeloma Using Lenalidomide | *protocol code and contact physician updated, CAP deleted* | *protocol code updated, CAP deleted* | -- |
| **SM \| Skin and Melanoma** | | | | |
| **SMAJPEM** | Adjuvant Treatment of Resected Stage IIB to IV NED Melanoma Using Pembrolizumab | *title, eligibility, exclusions, phone number and references updated* | *n/a* | *n/a* |
| **SMAJPEM6** | Adjuvant Treatment of Resected Stage IIB to IV NED Melanoma Using 6-Weekly Pembrolizumab | *title, eligibility, exclusions, phone number and references updated* | *n/a* | *n/a* |

## 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 | | |
| CST Bulletin: http://www.bccancer.bc.ca/health-professionals/clinical-resources/systemic-therapy/cst-bulletin | | |
| Systemic Therapy Update Editor | 604-877-6000 x 672649 | bulletin@bccancer.bc.ca |
| Oncology Drug Information<br>Cancer Drug Manual Editor<br>Pharmacy Oncology Certification<br>Nurse Educators | 604-877-6275<br>250-519-5500 x 693742<br>250-712-3900 x 686820<br>604-877-6000 x 672638 | druginfo@bccancer.bc.ca<br>nbadry@bccancer.bc.ca<br>rxchemocert@bccancer.bc.ca<br>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<br>Professional Practice, Nursing<br>Provincial Systemic Therapy | 604-877-6000 x 672247<br>604-877-6000 x 672623<br>604-877-6000 x 672247 | mlin@bccancer.bc.ca<br>BCCancerPPNAdmin@ehcnet.phsa.ca<br>mlin@bccancer.bc.ca |
| BC Cancer – Abbotsford<br>BC Cancer – Kelowna<br>BC Cancer – Prince George<br>BC Cancer – Surrey<br>BC Cancer – Vancouver<br>BC Cancer – Victoria | 604-851-4710<br>250-712-3900<br>250-645-7300<br>604-930-2098<br>604-877-6000<br>250-519-5500 | toll free 877-547-3777<br>toll free 888-563-7773<br>toll free 855-775-7300<br>toll free 800-523-2885<br>toll free 800-663-3333<br>toll free 800-670-3322 |
| Community Oncology Network (CON) sites: To update your contact information, please contact: bulletin@bccancer.bc.ca | | |

## Editorial Review Board