BC Cancer Protocol Summary for Peptide Receptor Radionuclide Therapy (PRRT) using Lutetium ^{177}Lu-Dotatate (LUTATHERA) for Treatment in Patients with Somatostatin Receptor Positive Neuroendocrine Tumours

Protocol Code	*UGIPRRT*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Well-differentiated neuroendocrine tumour of the pancreas or mid-gut that is unresectable or metastatic,
- Somatostatin receptor avidity on appropriate imaging,
- Radiographic progression on somatostatin analogue or contraindication or intolerance to somatostatin analogue, and
- A BC Cancer Compassionate Access Program (CAP) request with appropriate clinical information for each patient must be approved prior to treatment

Patients should have:

- ECOG 0 to 2
- Life expectancy of at least 3 to 6 months
- Adequate renal function (Creatinine Clearance greater than or equal to 40 mL/min)
- Adequate marrow reserve (ANC greater than or equal to 1.0 x 10^9/L and platelets greater than or equal to 75 x 10^9/L)

EXCLUSIONS:

Patients must not have:

- Lung, or hindgut neuroendocrine tumors
- Current pregnancy or be lactating. For women of childbearing potential and male patients who are not sterile, appropriate contraception is required
- Poorly controlled congestive heart failure or diabetes mellitus
- Inability to interrupt short acting octreotide due to symptoms for more than 24 hours before and 24 hours after infusion
- Urinary incontinence or inability to move easily to evacuate bladder during infusion
- Severe hepatic impairment (total bilirubin greater than 3 times upper limit of normal or albumin less than 30 g/L with increased prothrombin time (PT)

CAUTION:

- Patients with significant peritoneal disease

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TESTS:

Currently, PRRT is only available at BC Cancer – Vancouver Centre. If a patient meets the criteria and is interested, able, and willing to travel to Vancouver for treatment, the referring provider must complete the following baseline investigations prior to submitting a referral:

- Baseline labs: CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, urea, uric acid, albumin, total bilirubin, ALT, alkaline phosphatase, GGT, LDH, TSH, random glucose, INR, PT, Chromogranin-A (CgA)
- Functional imaging demonstrating somatostatin receptor positive disease within 6 months of planned therapy start date
- Cross sectional imaging showing progression of disease within the prior 6 months
- A transthoracic echocardiogram within the past year evaluating for valvular heart disease
- An in-person history and physical with their referring provider within 3 months (exclusion possible for remote patients or those from Yukon)

After baseline investigations are complete, follow these steps for referral:

- Approval for treatment funding should be submitted through the BC Cancer Compassionate Access Program (CAP) by the referring provider.
- After CAP has been approved, the Vancouver PRRT/Nuclear Medicine team will arrange consultation to assess/confirm appropriateness of PRRT.
- During PRRT, patients will be reviewed by the treating team in Vancouver, but the treating oncologists at other sites are requested to continue managing long acting somatostatin analogue prescriptions and supportive medications, and to facilitate a transfer of care after completion of PRRT.
- For any questions, please contact Dr. Jonathan Loree (Medical Oncology) or Dr. Don Wilson (Nuclear Medicine).

- Two weeks prior to each treatment: CBC & Diff, platelets, creatinine, sodium, potassium, calcium, magnesium, albumin, total bilirubin, ALT, INR
- If clinically indicated: CgA, HbA1c, PT, ECG

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PREMEDICATIONS:

- ondansetron 8 mg PO or IV 30 minutes prior to therapy
- 2.5% Lys-Arg Amino acid IV infusion at a rate of 250 mL/hour or as suggested by treating physician starting 30 minutes before ^{177}Lu-Dotatate (LUTATHERA) infusion, continuing during ^{177}Lu-Dotatate (LUTATHERA) infusion and for at least 3 hours after ^{177}Lu-Dotatate (LUTATHERA) infusion.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
Lutetium ^{177}Lu-Dotatate (LUTATHERA)	7.4 GBq/200 mCi over 30 minutes every 8 weeks	Intravenous infusion* * Initiate infusion at 50 mL/h – 100 mL/h for 5-10 min, then increase infusion rate to 200 mL/h – 300 mL/h until completed. Continue infusion until the level of radioactivity in the vial becomes stable for at least five minutes. This agent will be administered in an appropriately shielded room under the supervision of a physician and personnel qualified for administration of therapeutic isotopes. The infusion must be performed in a facility with valid Canadian Nuclear Safety Commission license for administration of therapeutic ^{177}Lu.

- Repeat every 8 weeks for maximum 4 doses, unless disease progression or unacceptable toxicity.
- Patients with adverse effects related to treatment can wait up to 16 weeks between treatments for recovery.
- For patients receiving a long acting somatostatin analogue to control symptoms from a functional tumor, injections should be given on Day 2 following ^{177}Lu-Dotatate (LUTATHERA) intravenous infusion and should be avoided for at least 4 weeks prior to PRRT.

- Highly symptomatic patients may be treated with short acting somatostatin analogues during the 6 weeks until 24 hours preceding ^{177}Lu-Dotatate (LUTATHERA) administration.
- Octreotide may be required for treatment of carcinoid flare (see Precautions).

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DOSE MODIFICATIONS:

A. Dose Modification for HEMATOLOGIC Toxicity

Prior to Cycle (Day 1)	Toxicity		Dose Modification
	Grade	Range values	
Neutropenia ANC ($x10^9$/L)	1	Greater than or equal to 1.5	100% dose: 7.4 GBq (200 mCi)
	2	1.0 to less than 1.5	
	3	0.5 to less than 1.0	• Hold treatment. Perform weekly CBC until complete or partial resolution (Grade 0, 1 or 2) • Then resume at 3.7 GBq (100 mCi). • If reduced dose does not result in Grade 3 or 4 neutropenia, increase dose back to 7.4 GBq (200 mCi) for next treatment.
	4	Less than 0.5	
	Recurrent Grade 3 or 4		Permanently discontinue
Thrombocytopenia Platelets ($x10^9$/L)	1	Greater than or equal to 75	100% dose: 7.4 GBq (200 mCi)
	2	50 to less than 75	• Hold treatment. Perform weekly CBC until complete or partial resolution (Grade 0 or 1). • Then resume at 3.7 GBq (100 mCi). • If reduced dose does not result in Grade 2, 3 or 4 thrombocytopenia, increase dose back to 7.4 GBq (200 mCi) for next treatment.
	3	25 to less than 50	
	4	Less than 25	
	Recurrent Grade 2, 3 or 4		Permanently discontinue
Anemia Hgb (g/L)	1	Greater than or equal to 100	100% dose: 7.4 GBq (200 mCi)
	2	80 to less than 100	
	3	Less than 80	• Hold treatment. Perform weekly CBC until complete or partial resolution (less than Grade 3) • Then resume at 3.7 GBq (100 mCi). • If reduced dose does not result in Grade 3 or 4 anemia, increase dose back to 7.4 GBq (200 mCi) for next treatment.
	4	Life threatening consequences	
	Recurrent Grade 3 or 4		Permanently discontinue

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B. Dose Modification for NON-HEMATOLOGIC Toxicity

<table>
<tr><th rowspan="2">Prior to Cycle (Day 1)</th><th colspan="2">Toxicity</th><th rowspan="2">Dose Modification</th></tr>
<tr><th>Grade</th><th>Range values</th></tr>
<tr><td rowspan="4">Hepatotoxicity Bilirubin (micromol/L)</td><td>1</td><td>Less than or equal to 1.5 x ULN</td><td rowspan="2">100% dose: 7.4 GBq (200 mCi)</td></tr>
<tr><td>2</td><td>Greater than 1.5 to 3 x ULN</td></tr>
<tr><td>3</td><td>Greater than 3 to 10 x ULN</td><td rowspan="3">• Hold treatment. Perform weekly chemistry analysis until complete or partial resolution (Grade 0 or 1)
• Then resume at 3.7 GBq (100 mCi).
• If reduced dose does not result in Grade 3 or 4 bilirubinemia/hepatotoxicity, increase dose back to 7.4 GBq (200 mCi) for next treatment.</td></tr>
<tr><td>4</td><td>Greater than 10 x ULN</td></tr>
<tr><td rowspan="2">Hepatotoxicity</td><td colspan="2">Albumin less than 30 g/L with INR greater than 1.5</td></tr>
<tr><td colspan="2">Recurrent hepatotoxicity</td><td>Permanently discontinue</td></tr>
<tr><td rowspan="4">Renal Toxicity Creatinine Clearance (CrCl) (mL/min)</td><td colspan="2">CrCl less than 40</td><td rowspan="3">• Hold treatment. Perform weekly chemistry analysis until complete resolution.
• Then resume at 3.7 GBq (100 mCi).
• If reduced dose does not result in renal toxicity, increase dose back to 7.4 GBq (200 mCi) for next treatment.</td></tr>
<tr><td colspan="2">40% increase in baseline serum creatinine</td></tr>
<tr><td colspan="2">40% decrease in baseline CrCl</td></tr>
<tr><td colspan="2">Recurrent renal toxicity</td><td>Permanently discontinue</td></tr>
<tr><td rowspan="3">Other Non-Hematologic Toxicity</td><td colspan="2">Grade 1 or 2</td><td>100% dose: 7.4 GBq (200 mCi)</td></tr>
<tr><td colspan="2">Grade 3 or 4</td><td>• Hold treatment until complete resolution (Grade 0 to 2)
• Then resume at 3.7 GBq (100 mCi).
• If reduced dose does not result in Grade 3 or 4 toxicity, increase dose back to 7.4 GBq (200 mCi) for next treatment.</td></tr>
<tr><td colspan="2">Recurrent Grade 3 or 4</td><td>Permanently discontinue</td></tr>
</table>

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PRECAUTIONS:

1. Patient must be kept in **radiation isolation** for a period of 4-5 hours following administration and have a measured discharge dose rate of less than 25 microSv/hr at 1 meter distance.

2. **Prevention of extravasation** is essential and the IV-line patency must be tested prior to administration of ^{177}Lu-Dotatate (LUTATHERA). Rapid intervention must be implemented if extravasation occurs, noted by local swelling and pain at the injection site. If this occurs, the infusion must be stopped immediately and the infusion site must be treated with warm packs, compression and elevation. Exercise to increase blood flow to the affected limb may also be useful to reduce the local dose. Infiltration must be reported to the radiation safety officer and nuclear medicine physician for monitoring and calculation of skin dose.

3. Patients should be monitored for symptoms of **carcinoid flare** such as flushing, diarrhea, hypotension, bronchoconstriction or unstable vitals as tumor-related hormonal release may occur.

   Octreotide can be administered along with fluids, corticosteroids, and electrolytes as indicated.

   Suggested dose (call provider after first dose of octreotide):
   - octreotide 100 mg subcutaneously STAT, may repeat in 5 minutes x 1 PRN (total dose 200 mcg),

   OR
   - octreotide 200 mcg subcutaneously STAT x 1,

   THEN
   - octreotide 100 mcg to 200 mcg subcutaneously every 1 hour PRN

   Ongoing long acting somatostatin therapy:
   - Patients with carcinoid syndrome should be continued on a somatostatin analogue. For patients without carcinoid syndrome, a case by case discussion about whether to continue should be had until further evidence is available.

4. The room must be monitored for radioactivity contamination after each treatment by qualified nuclear medicine personnel under the supervision of a medical physicist.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

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References:

1. Strosberg J, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017;176:125-135.
2. Kwekkeboom DJ, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124-30.
3. Sadowski S, Neychev V, CorinaMillo et al. Prospective Study of 68Ga-DOTATATE Positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. J Clin Oncol 2016;34:588-596.
4. Clement D, Navalkissoor S, Srirajaskanthan R, et al. Efficacy and safety of ^{177}Lu-DOTATATE in patients with advanced pancreatic neuroendocrine tumours: data from the NETTER-R international, retrospective study. Eur J Nucl Med Mol Imaging. 2022 Aug;49(10):3529-3537.
5. Lutetium (177Lu) Oxodotreotide (Lutathera) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies October 2022; 2(10):1-24.
6. Mitjavila M, Jimenez-Fonseca P, Belló P, et al. Efficacy of [^{177}Lu]Lu-DOTATATE in metastatic neuroendocrine neoplasms of different locations: data from the SEPTRALU study. Eur J Nucl Med Mol Imaging. 2023 Jul;50(8):2486-2500.

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