PRRT in Canada

The latest options for Canadian patients & what is around the corner?

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Disclosure

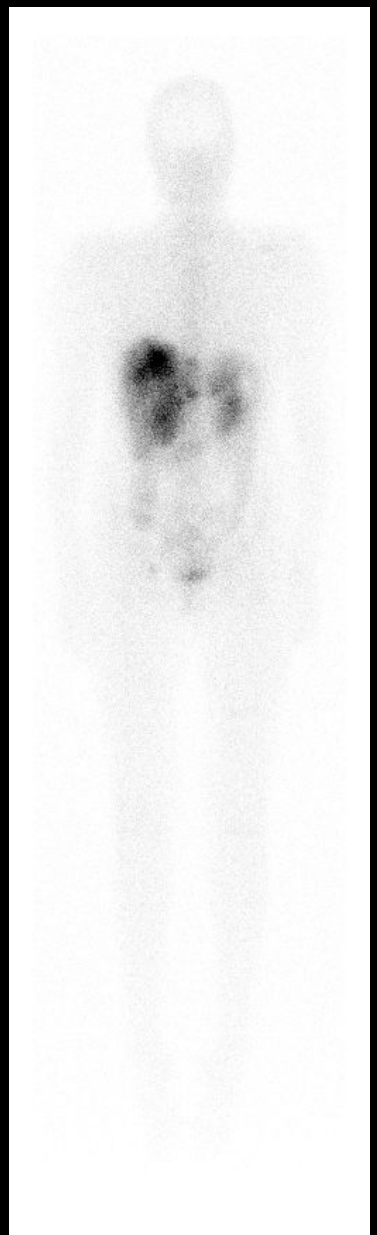
- None

Peptide receptor radionuclide therapy (PRRT)

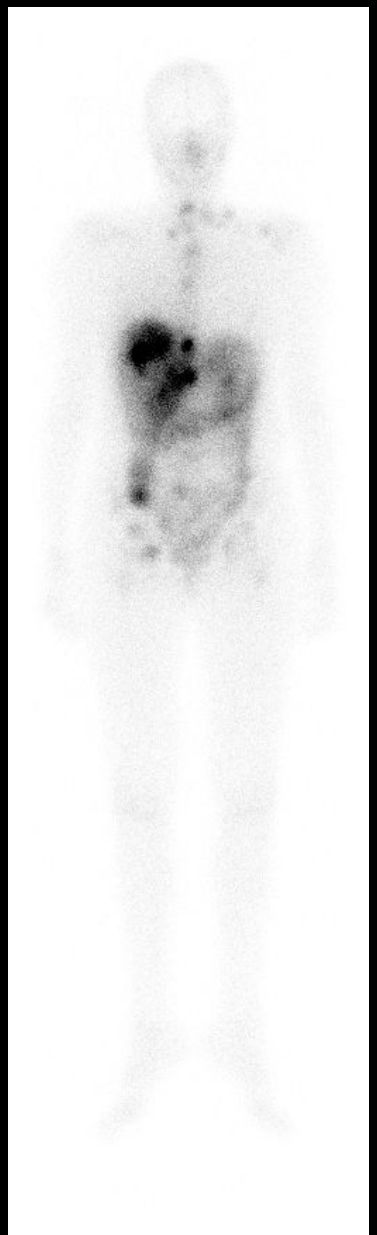
- Internal radiotherapy with radiolabelled somatostatin analogs
  - Targeting the somatostatin receptor overexpressed by NETs
- Palliative targeted therapy for:
  - Progressive and/or symptomatic, unresectable NET
  - Positive on Octreoscan or ^{68}Ga-PET
- Developed in European centers over the last 25 years
  - ^{111}In-octreotide (Octreoscan)
  - ^{90}Y-octreotide (DOTATOC)
  - **^{177}Lu-octreotate** (DOTATATE, LuTate, Lutathera)
- Theranostic approach: *"what you see is what you treat"*

CNETS CANADA

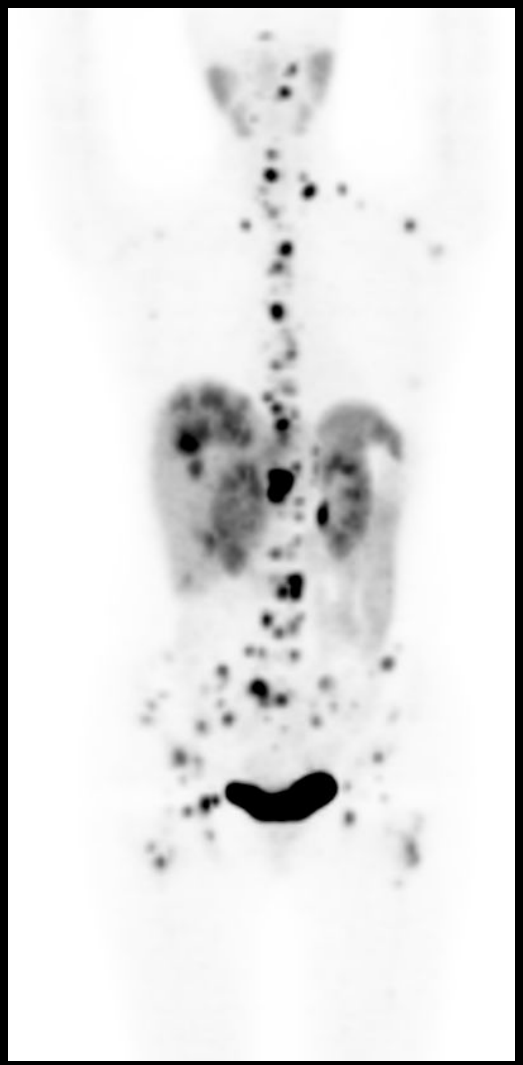
^{111}In-octréotide



^{177}Lu-octréotate



^{68}Ga-octréotate



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^{177}Lu-octreotate PRRT

- Efficacy (310 patients)

Complete response	Partial response	Minor response	Stable disease	Progressive disease
2%	28%	16%	35%	20%

  - Disease-specific survival: 11 mo. for PD *vs.* >48 mo. for SD/remission
  - Global survival gain estimate: 23-69 months (vs. historical controls)
- Side-effects and toxicity (504 patients)
  - Acute: Nausea: 25 %, Vomiting: 10 %, Pain:10 %, Hormonal crisis:1.2%
  - Subacute: Transient hematological toxicity (grade 3-4): 9.5 %
  - Serious/delayed: 1.8 %
    - 2 pts: renal impairment
    - 3 pts: severe hepatic toxicity (2 pts recovered)
    - 5 pts: myelodysplastic syndrome

Kwekkeboom et al. *J Clin Oncol 2008* 26:2124-30

PRRT improves Quality of life

- 265 pts, Quality of Life questionnaire
- Quality of Life significantly improved in 36%
- Specific symptoms improved in 44 to 77%
- Independent of objective response

Khan et al. *J Nucl Med 2011 52:1361-68*

NETTER-1 study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

ABSTRACT

BACKGROUND

Patients with advanced midgut neuroendocrine tumors who have had disease progression during first-line somatostatin analogue therapy have limited therapeutic options. This randomized, controlled trial evaluated the efficacy and safety of lutetium-177 (^{177}Lu)–Dotatate in patients with advanced, progressive, somatostatin-receptor–positive midgut neuroendocrine tumors.

METHODS

We randomly assigned 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors to receive either ^{177}Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (^{177}Lu-Dotatate group) or octreotide LAR alone (1

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Strosberg at the Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, FL 33612, or at jonathan.strosberg@moffitt.org.

*A complete list of investigators in the Neuroendocrine Tumors Therapy (NETTER-1) trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;376:125-35.
DOI: 10.1056/NEJMoa1607427

CNETS CANADA

Strosberg J et al. *N Engl J Med* 2017; 376:125-135

NETTER-1 study

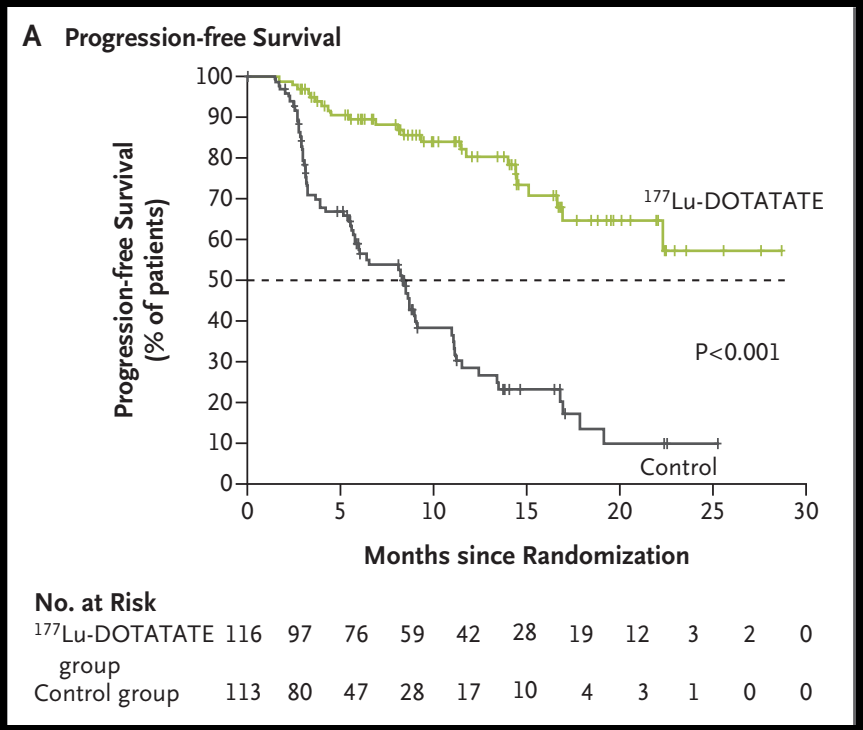
- Multicenter randomised clinical trial
- 229 patients with progressive midgut NET
  - on Sandostatin LAR 20-30 mg
- Randomization between:
  - Hi-dose Sandostatin LAR (60 mg), or
  - ^{177}Lu-octréotate PRRT
- Endpoints:
  - 1^{ary}: Progression-free survival (PFS)
  - 2^{ary}: Objective response; Overall survival; Safety

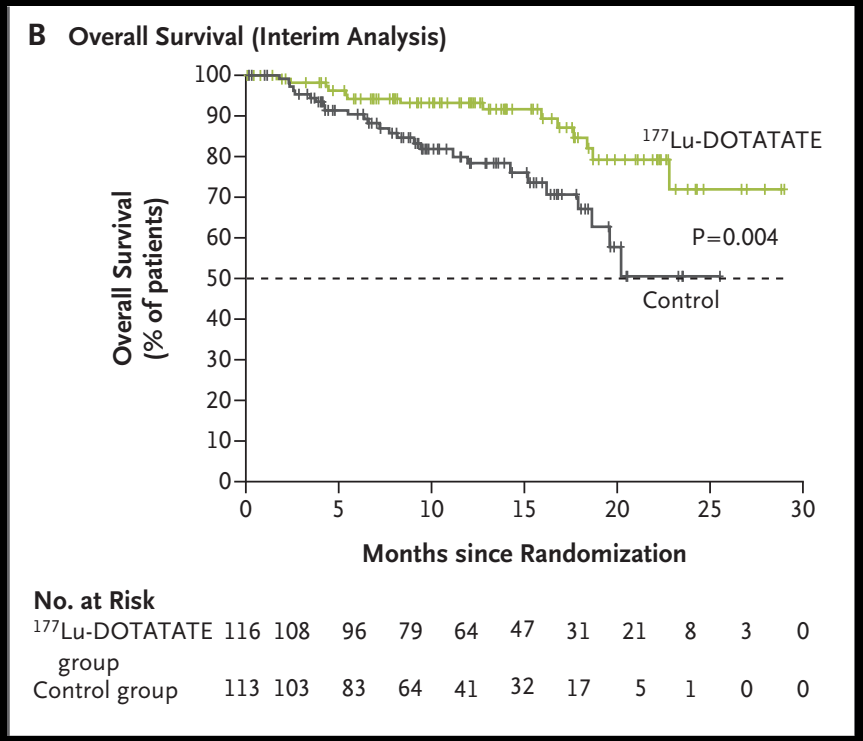
CNETS CANADA

Strosberg J et al. *N Engl J Med* 2017; 376:125-135

NETTER-1: Survival

- PFS: Not reached *vs.* 8.4 mois
  - HR 0.21 (0.13 – 0.33; *P*<0.001)
- Taux PFS @20 mois: 65.2 *vs.* 10.8%
- OS (interim): 14 *vs.* 26 deaths
  - HR 0.40 (*P*=0.004)





Strosberg J et al. *N Engl J Med* 2017; 376:125-135

NETTER-1: Response and Toxicity

- ORR: 18% vs. 3%

Table 2. Objective Tumor Response.*

Response Category	^{177}Lu-Dotatate Group (N = 101)	Control Group (N = 100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

- Side effects: rarely severe (<3%)
  - Most common: Nausea/vomitting, Fatigue
    - Abdominal pain and diarrhea not more frequent than with Sandostatin only
- Hematological toxicity:
  - Most common: thrombopenia and lymphopenia
    - No clinical consequences
- No significant renal toxicty @ 14 mo.

CNETS CANADA

Strosberg J et al. *N Engl J Med* 2017; 376:125-135

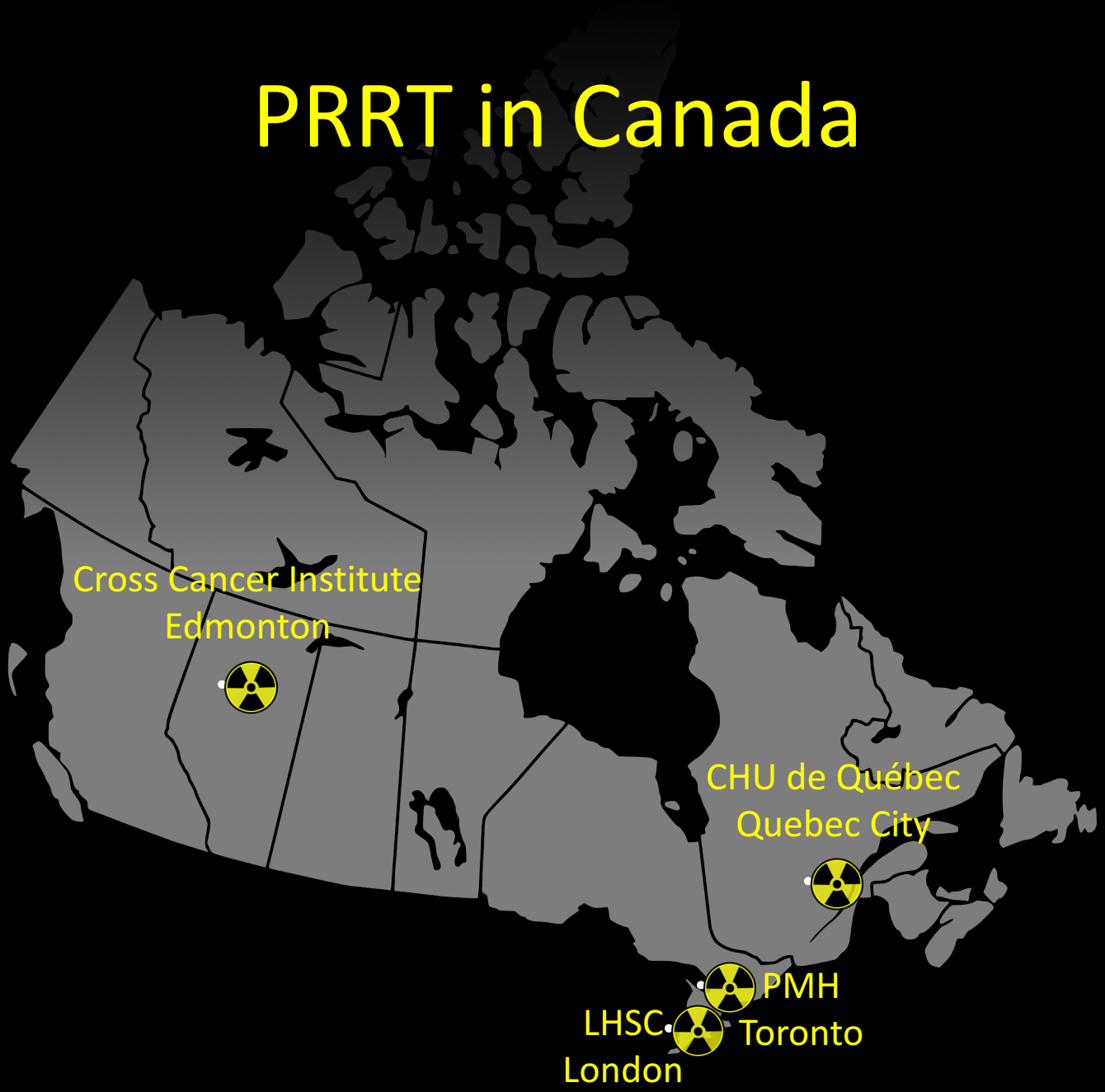
NETTER-1

- PRRT efficacy now “proven” with highest level of evidence
  - FDA approval pending
    - Application to Health Canada likely to follow
  - Will be indicated only for midgut NET
    - We “know” that PRRT is even more effective against pancreatic NET…

PRRT in Canada

- ^{177}Lu PRRT has been practiced since 2010 in Canada
  - Initially under Special Access Program
    - Case-by-case requests to Health Canada
    - Last resort option
  - Since 2014 under publicly-funded clinical trials

PRRT in Canada



Cross Cancer Institute

Edmonton, AB

- ^{177}Lu PRRT since 2010
  - 1342 cycles administered to 248 patients
    - 53 patients under SAP
    - 195 patients under trial
  - Initially under SAP, then under clinical trial since 2014
- Protocol:
  - 4 induction cycles $\leq$ 5.6 GBq/cycle q 3 mo.
  - $\leq$ 8 maintenance cycles $\leq$ 3.7 GBq/cycle q 6-10 mo
  - In-patient procedure (24h)
- Encouraging preliminary results:
  - Longer than expected PFS (not reached at 59 mo.)
  - Toxicities within known range
- Ongoing experience with ^{131}I-MIBG

CNETS CANADA

London Health Sciences Center

London, ON

- ^{177}Lu PRRT since 2011
  - Prior experience with ^{111}In-octreotide PRRT
  - 452 ^{177}Lu-octreotate cycles administered
  - Initially under SAP
  - Local trial ~2014–2016 (following Edmonton protocol)
  - Joined the Cancer Care Ontario trial 2017/01
- Current protocol: CCO (next slide)
  - Transitioned to mostly out-patient treatments
- Ongoing experience with ^{131}I-MIBG

CNETS CANADA

Princess Margaret Hospital

Toronto, ON

- PRRT started in August 2016 under the Cancer Care Ontario Trial
  - 15 patients treated to date at PMH
    - 34 cycles delivered
    - 3 patients completed 4 cycles
- Protocol:
  - Fixed activity at 1st cycle (200 mCi)
  - Personalized injected activity at folowing cycles to deliver 23 Gy to the kidney (max 300 mCi)
  - Scan up to 3 days post-treatment for dosimetry
  - Out-patient procedure
- Results:
  - Activity escalation in 57%
  - Same activity (200 mCi) in 14%
  - Activity reduction in 28%

CNETS CANADA

CHU de Québec – Université Laval

Quebec City, QC

- PRRT started in 2012 under SAP
  - Initially under SAP
    - 124 empiric cycles administered in 36 patients
  - Since 2016, under a clinical trial
    - 93 personalized cycles in 37 patients
- Protocol:
  - All cycles personalized to deliver 23 Gy to kidney
    - Intra-arterial injection allowed
  - Scan up to 3 days post-treatment for dosimetry
  - Unlimited maintenance cycles offered to responders
  - Out-patient procedure
- Results:
  - Appears safe on the short-term
  - Significant activity/dose increase over fixed-activity regime
- Ongoing experience with ^{131}I-MIBG

CNETS CANADA

PRRT in Canada - Summary

	Edmonton	London	Toronto	Quebec City
No. of patients	248	~115	15	62
Dosing	100-150 mCi	Cycle 1: 200 mCi Cycles 2-4: Personalized		Personalized
Max. act./cycle	150 mCi	300 mCi		Unlimited
Scanning	At 24h	For 3 days		For 3 days
In/out-patient	In	Out		Out
Maintenance	Yes	No?		Yes
Eligibility	All Canadians	Ontarians only		All Canadians

CNETS CANADA

PRRT in Canada - Summary

- Significant collective medical experience in Canada
- Some differences between centers/trials:
  - Relatively minor
  - All protocols are designed with safety and efficacy in mind
- More in common than differences: *It's PRRT after all!*
- Innovative trials:
  - We avoid barely replicating old trials
  - Less restrictive than SAP or industry trials
  - **All NET** subtypes eligible
- Publicly-funded
  - No commercial interests
  - Limited resources

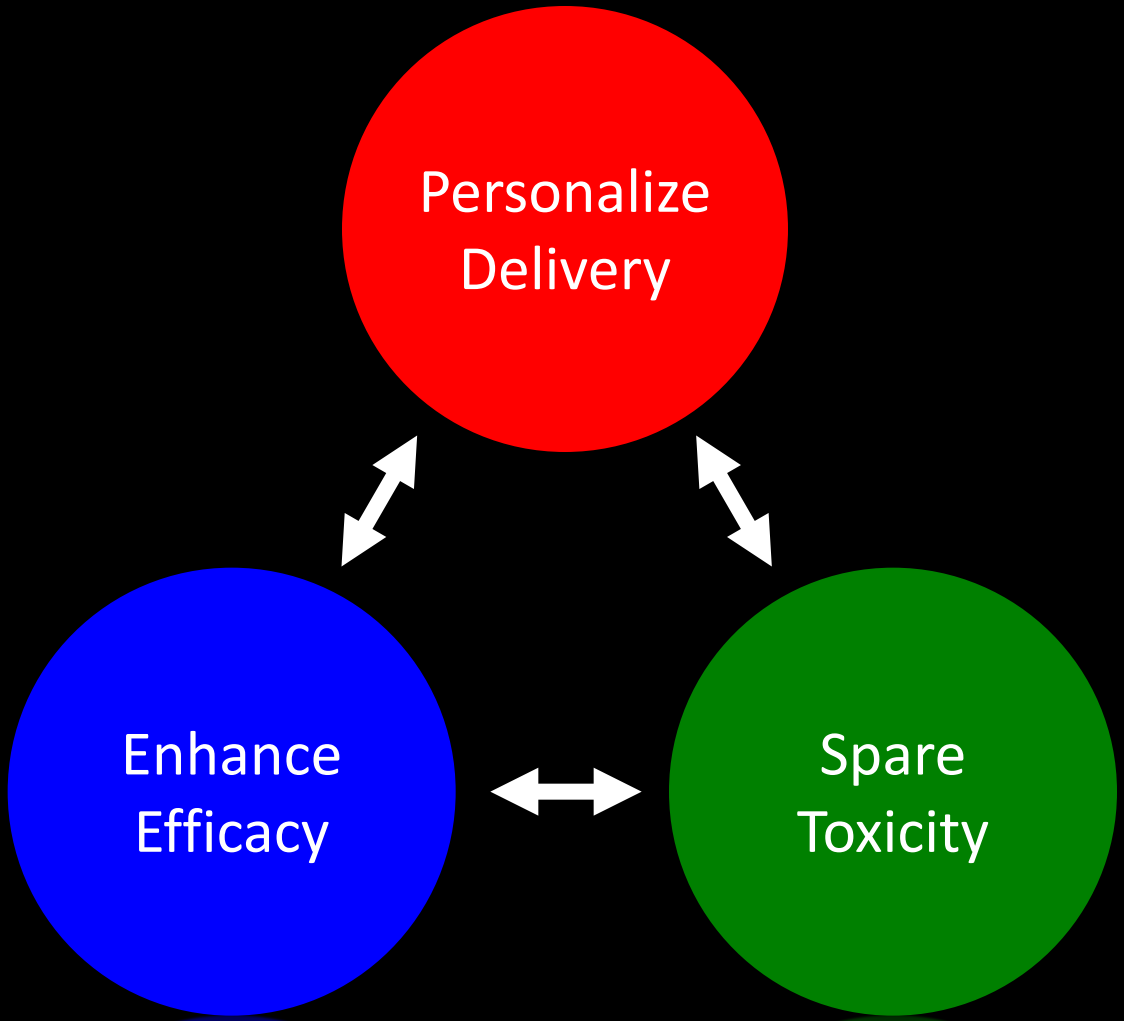
CNETS CANADA

What is around the corner?

- Lutathera (^{177}Lu-octreotate) likely to be marketed in Canada
  - May allow more centers to provide PRRT
    - Balance between geographic coverage and expertise
  - May be restricted to approved indication and empiric dosage
    - Midgut NET, 200 mCi per cycle
- Other pharma (e.g. Ipsen) are starting PRRT trials with other PRRT radiopharmaceuticals
  - Will Canadian sites be included?
  - Potential to improve PRRT efficacy
- Current publicly-funded trials should continue
  - Maintain access
  - Promote innovation (personalization)

CNETS CANADA

How to further improve PRRT of NET?



How to further improve PRRT of NET?

Personalize Delivery

- Adjust PRRT activity
  - Predictive factors
  - Dosimetry
- Adjust PRRT timing
  - Earlier/later in disease's course
  - Inter-cycle interval
- Select best RP
  - Peptide
  - Radionuclide
- Intra-arterial administration
  - Liver metastasis

Enhance Efficacy

- New peptides
  - Increased SSTR affinity
  - SSTR antagonists?
- "New" radionuclides
  - Particle energy
  - Alpha particles?
  - Combination??
- Radiosensitization
  - Chemotherapy
    - 5-FU
    - Capecitabine …
  - Biotherapy
    - PARP inhibitor?
    - Tyrosine kinase inhibitor?
    - mTOR inhibitor? …

Spare Toxicity

- New peptides
  - Lower critical organ uptake
- "New" radionuclides
  - Microdosimetric considerations
- Radiosensitization
  - Decrease PRRT activity
- Nephroprotection
  - Optimize amino acid administration
  - New agents?

CNETS CANADA

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CNETS CANADA

PRRT

- One of the most effective palliative therapy for progressive/symptomatic NET
  - Response rates, Survival, Quality of life
- « Proven » efficacy against midgut NETs
  - Role and optimum treatment sequence to be better defined for other NETs
- Available for all Canadian patients, all NETs
- Revival of the *THERANOSTIC* concept in nuclear medicine

Thank you

STCNE DU CANADA
SOCIÉTÉ DES TUMEURS Carcinoïdes-NeuroEndocrines DU CANADA

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