National Program on Radioligand Therapy for Prostate Cancer

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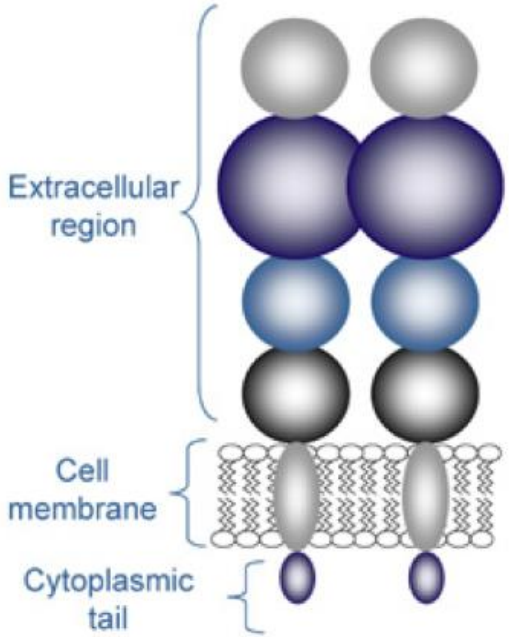
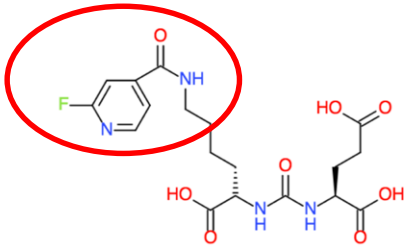
PSMA Background

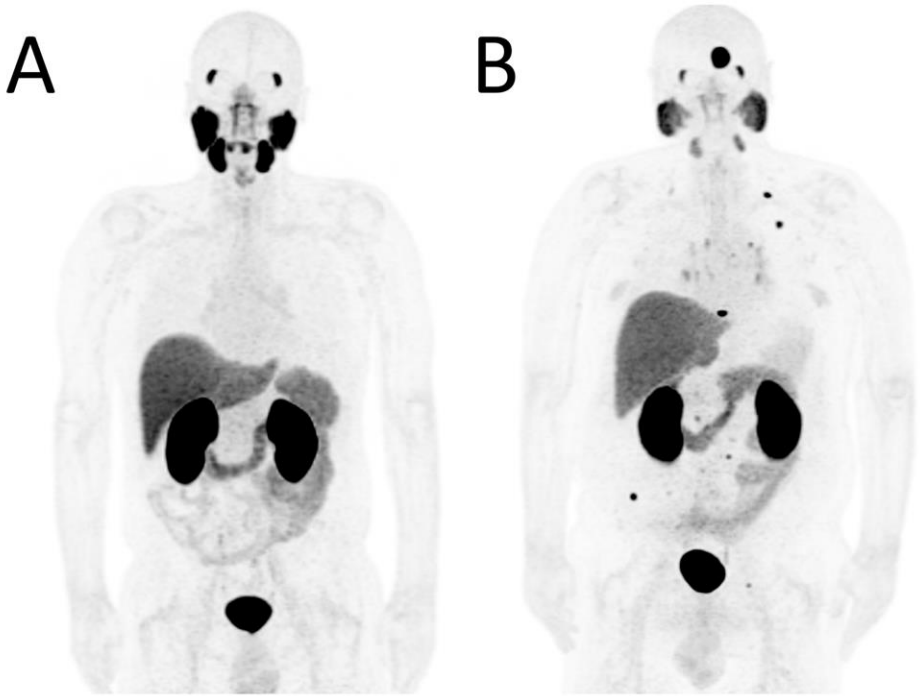
- Prostate specific membrane antigen (PSMA)
  - Gene on chromosome 11p in a region that is not commonly deleted in prostate cancer
  - Transmembrane protein expressed in prostatic tissue
    - 19-amino-acid internal portion, 24-amino-acid transmembrane portion, 707-amino-acid external portion
    - Enzymatic activity and acts as a glutamate-preferring carboxypeptidase
    - Internalization signal that allows internalization of the protein on the cell surface into an endosomal compartment



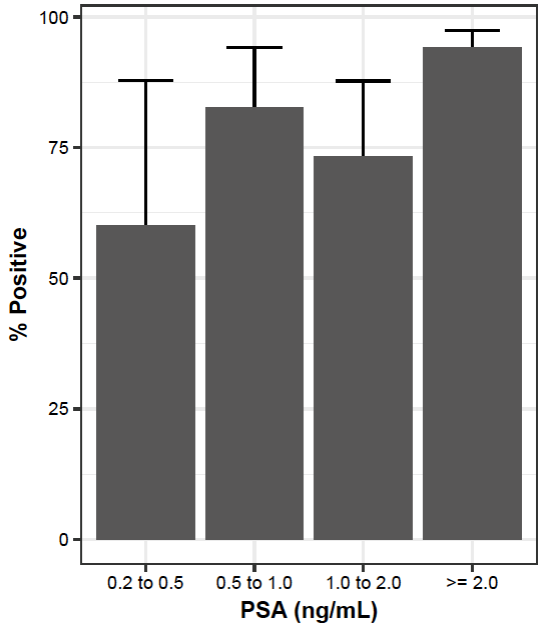
PSMA imaging at BC Cancer



^{18}F-DCFPyL

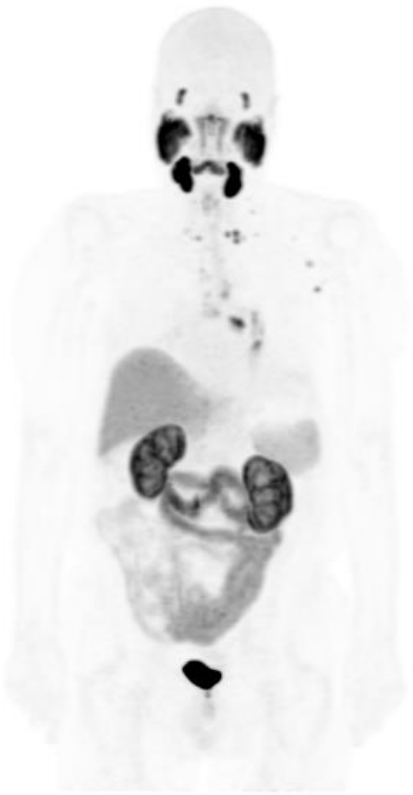


Detection of recurrent prostate cancer
BC Cancer experience

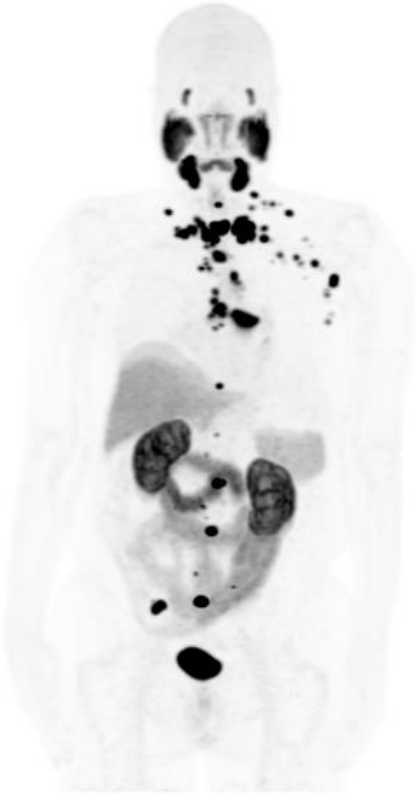


Data from interim analysis of first 200 subjects

Progression of prostate cancer



Baseline



8 months later

^{177}Lu-PSMA-617 Phase II Evidence

- 30 mCRPC patients after standard treatments treated with ^{177}Lu-PSMA-617
- Mean dose 7.5 GBq every 6 weeks up to 4 cycles
- Primary Endpoint: PSA response (≥50% decline) in 17 (57%) patients
- **ORR in 14/17 patients (82%)**
- Median PSA PFS 7.8 months, immature OS data
- Commonest adverse events (AEs):
  - Gr 1 xerostomia in 19 (63%)
  - Gr 3 or higher hematoxicity in 5 (17%), **reversible**

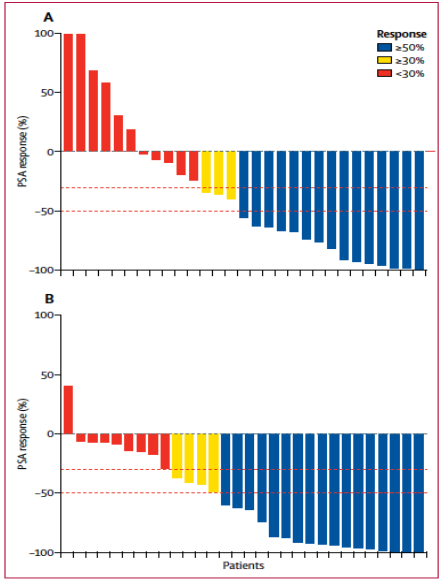


Figure 3: **(A) PSA response after 12 weeks* and (B) best PSA response from baseline**

	Grade 1–2	Grade 3	Grade 4	Grade 1–2, attributed to LuPSMA*	Grade 3 attributed to LuPSMA*	Grade 4 attributed to LuPSMA*
Dry mouth	26 (87%)	0	0	26 (87%)	0	0
Lymphocytopenia	12 (40%)	13 (43%)	0	11 (37%)	11 (37%)	0
Thrombocytopenia	12 (40%)	5 (17%)	3 (10%)	8 (27%)	3 (10%)	1 (3%)
Fatigue	16 (53%)	1 (3%)	0	15 (50%)	0	0
Nausea	15 (50%)	0	0	15 (50%)	0	0
Anaemia	7 (23%)	7 (23%)	0	4 (13%)	4 (13%)	0
Neutropenia	12 (40%)	2 (7%)	0	8 (27%)	2 (7%)	0
Pain	8 (27%)	3 (10%)	0	5 (17%)	1 (3%)	0
Vomiting	10 (33%)	0	0	10 (33%)	0	0
Anorexia	8 (27%)	0	0	7 (23%)	0	0
Dry eyes	5 (17%)	0	0	5 (17%)	0	0
Weight loss	3 (10%)	0	0	3 (10%)	0	0
Disseminated intravascular coagulation	0	1 (3%)	0	0	0	0
Oculomotor nerve disorder	1 (3%)	0	0	1 (3%)	0	0
Spinal fracture	0	1 (3%)	0	0	0	0
Hip fracture	0	1 (3%)	0	0	0	0

Data are n (%). Grade 1–2 adverse events occurring in ≥10% of the cohort and all grade ≥3 adverse events are presented. There were two grade 5 adverse events not attributed to LuPSMA: pneumonia (n=1), hepatic failure (n=1). LuPSMA=lutetium-177 prostate-specific membrane antigen-617. *Possibly, probably, or definitely according to Common Terminology Criteria for Adverse Events.

Table 3: **Treatment-emergent adverse events**

MS Hofman, et al. Lancet Oncol, 19(6): 825-833, 2018

Endocyte study – Vision Trial

- Randomized study of 750 men worldwide
- Patients with metastatic castration-resistant prostate cancer
- Positive PET scan with ^{68}Ga-PSMA-11
- Must have received prior novel androgen axis drug (abiraterone or enzalutamide)
- Must have received one or two taxane based chemotherapy regimen
- Adequate bone marrow and kidney function
- 2:1 randomization
  - 2 subjects 177Lu-PSMA-617
  - 1 subject best standard of care/supportive care
  - No cross-over
- Product manufactured in USA
- Opened in Vancouver in January 2019

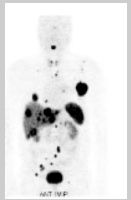
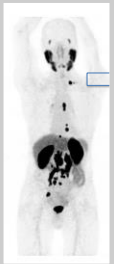
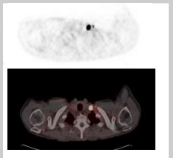
Objectives of the National Program

- Implement Lu-177 PSMA radiopharmaceutical production for prostate cancer clinical trials
- Conduct a randomized Phase 2 trial of ^{177}Lu-PSMA radioligand therapy vs docetaxel in men with castration resistant prostate cancer (CRPC), and optimizing quantitative imaging and dosimetry for personalized RLT
- Perform an economic analysis of targeted radionuclide therapy ^{177}Lu-PSMA for metastatic castration resistant prostate cancer

Specific Aims of the Program

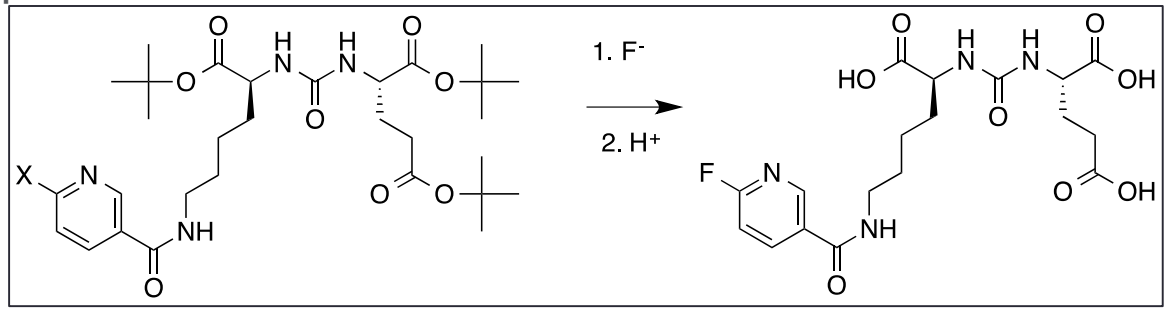
1. Implement Production and Distribution of PSMA radiopharmaceuticals for Canadian clinical trials
2. Conduct a randomized cross-over phase 2 trial of radioligand therapy (RLT) vs docetaxel
3. Perform an economic evaluation of RLT in mCRPC

Aim 1 – Implement Production and Distribution of PSMA radiopharmaceuticals for use in clinical trials

Prior Network Collaborations	Manufacturing and Distribution Expertise	NETs Experience	Growing Access to PSMA PET
			 
Shared production methods, QA, and regulatory filings	National distribution expertise	<u>Multiple</u> locations using Lu-177 DOTA-TATE/TOC	DCFPyL, ^{68}Ga-11
MITNEC	cpdc BC CANCER		**Published method developed by the MITNEC team**

Choice of Diagnostic Agent

- ^{18}F-DCFPyL is widely available in Canada thanks to the MITNEC program and a team effort to develop an automated production platform



EJNMMI Res. 2016; 6: 40

- We will also allow sites to use ^{68}Ga based agents to expedite the trials

Choice of Therapeutic Radioligand

- A number of PSMA radiotherapeutics were considered
- ^{177}Lu-PSMA-617, ^{177}Lu-PSMA I&T, ^{225}Ac-PSMA-617, ^{177}Lu-J591, others...
- The program decided to focus on beta emitters versus alpha emitters based on the more extensive clinical experience, availability of ^{177}Lu for multicentre studies, side effect profile
- ^{177}Lu-PSMA-617 selected based on data available and recommendation of expert review panel
- Agreement by Endocyte to provide GMP precursor for the study

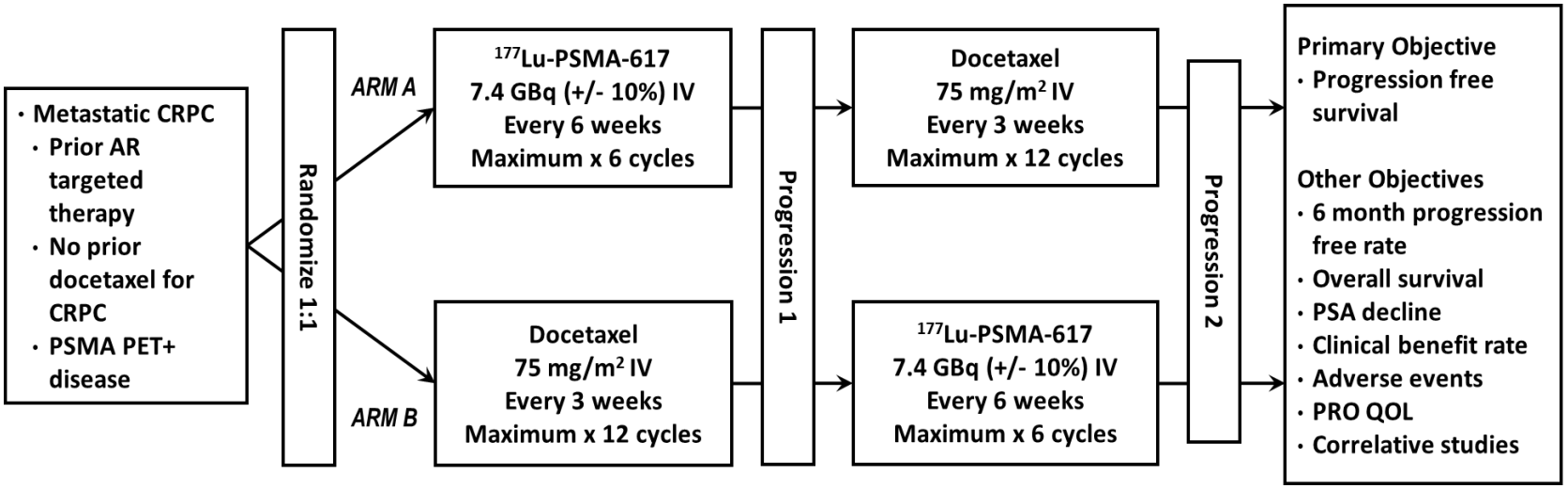
Aim 2

PLUDO*: A Randomized Phase II Study of ^{177}Lu-PSMA-617 vs Docetaxel in Patients with Metastatic Castration-Resistant Prostate Cancer and PSMA-Positive Disease

*Prostate Lutetium Docetaxel

PLUDO: Randomized Phase II Study of ^{177}Lu-PSMA-617 vs Docetaxel

Study Schema



- 200 participants will be randomized in a 1:1 ratio to either 177Lu-PSMA or docetaxel
- Assuming 24 months of accrual and a 12-month minimum follow-up time, a 10% non-evaluable rate, and 152 events, the study will have a power of 0.80 with a 1-sided alpha of 0.05 to detect a PFS difference with a hazard ratio of 0.67 assuming a median PFS of 6 vs 9 months

Study Objectives

- **Primary Objective**
  - To compare the progression free survival of PSMA-positive mCRPC patients treated with ^{177}Lu-PSMA radioligand therapy versus docetaxel
- **Secondary Objectives**
  - Proportion of patients that are progression free at 6 months as defined by PSA, objective disease, or symptoms
  - Overall survival (OS)
  - Clinical benefit rate (CBR; PR, CR, SD >24 weeks)
  - Proportions of patients with decreased PSA from baseline and magnitude of change from baseline
  - Adverse event (AE) profile of protocol therapy (CTCAE v4.03)
  - Patient reported quality-of-life (QoL) while on treatment with 177Lu-PSMA RLT and docetaxel
- **Exploratory Objectives**
  - To explore biomarkers of response and resistance using cell free DNA (cfDNA)
  - To retrospectively explore a dosimetry-based approach to determine injected activity

Key Inclusion Criteria

- Progression on treatment with abiraterone and/or enzalutamide, or similar agents (e.g. apalutamide).
- Evidence of PSMA-positive disease on PSMA PET/CT imaging
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
- Biopsy-proven prostate cancer with no evidence of small cell component
- Prior orchiectomy, or if on LHRH agonist/antagonist, then testosterone < 1.7 nmol/L at screening visit (and meeting these criteria through the study)
- Evidence of biochemical or imaging progression in the setting of surgical/medical castration
- Adequate bone marrow and renal function

Key Exclusion Criteria

- Prior treatment with docetaxel*, cabazitaxel or other radionuclide therapy
- More than one line of systemic therapy for mCRPC disease
- Other active cancer or co-morbidities that could interfere with safe RLT delivery
- Radiotherapy to target lesions ≤ 12 weeks ago or to more than 25% of bone marrow
- Known brain metastases or epidural disease (unless treated and stable for ≥ 6 months)
- Major surgery within 4 weeks of starting study treatment
- History of risk factors for xerostomia (i.e. head and neck radiation, Sjögren's disease) or pre-existing xerostomia

*Except in the context of castration sensitive disease in combination with ADT

Progression

- Radiologic progression
  - RECIST v1.1 criteria for measurable disease
  - Appearance of ≥ 2 new bone lesions on whole body bone scan confirmed on a subsequent scan (as per PCWG3 criteria)
- Clinical progression
  - Worsening of cancer-related symptoms mandating a change in anti-cancer therapy (e.g. radiation or chemotherapy)
  - Disease related ≥ 2 level decrease in ECOG PS

PLUDO: Randomized Phase II Study of ^{177}Lu-PSMA-617 vs Docetaxel

- A survey was administered October 2018 to CCTG Genitourinary Disease Site Committee members.
- A summary of 26 respondents is below:
  - Interested Centres 21
  - Interested Centres with resources to perform the PSMA PET-CT 10
  - Estimated annual eligible patient population - sites with PSMA PET-CT 217 – 405*
  - Estimated annual accrual - sites with PSMA PET-CT 89 – 187*

* min-max

Administered Activity

- (BSA)-adjusted IA of 7.4 GBq/1.73m^2 per cycle
- Up to 6 cycles, with each cycle separated by 6 weeks
- A 25% reduction in baseline IA will be adopted in subjects with grade 2 bone marrow or renal dysfunction.
- The IA of subsequent cycle(s) will be reduced by 25% in subjects with transient grade 3-4 toxicity (or discontinued as clinically warranted).
- Two post treatment planar and SPECT/CT after first cycle (18-30 hours; 72:96 hours)
- Single post treatment planar and SPECT/CT scan for subsequent cycles

Imaging and Lab Studies

- Baseline PET/CT scan with ^{18}F-DCFPyL,^{68}Ga-PSMA-11 or comparable PSMA PET imaging radiopharmaceuticals (such as ^{18}F-PSMA-1007)
- Subsequent post-treatment PET/CT scan funded separately via CIHR grant
- CT, bone scintigraphy at baseline and every 12 weeks
- Blood chemistry, CBC, testosterone, PSA every 3 weeks
- ctDNA (cell free DNA) collected at baseline and every 12 weeks to determine mechanisms of resistance

Aim 3: Economic Analysis of Radioligand Therapy

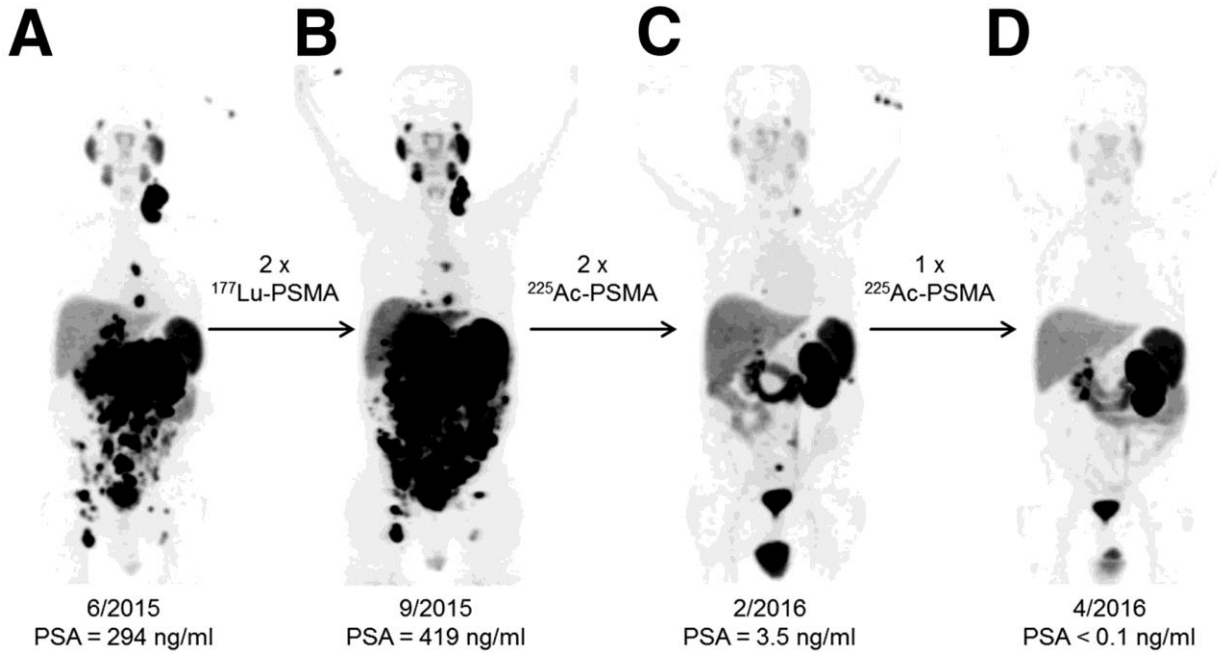
- **HYPOTHESIS**
  - Compared to docetaxel, ^{177}Lu-PSMA could be an economically attractive option for men with mCRPC as a second-line treatment from the public health care payer and societal perspective.
- **Primary Objective**
  - To examine the cost-effectiveness of ^{177}Lu-PSMA compared to docetaxel in men with mCRPC from the perspective of public health care payer and society in Canada using data from the trial over the study period.
- **Secondary Objectives**
  - To examine the “long-term” cost-effectiveness of ^{177}Lu-PSMA compared to docetaxel in men with mCRPC from the perspective of public health care payer and society in Canada.
  - To obtain information on mCRPC from administrative databases in British Columbia (BC) and Ontario (such as probability of survival, response rate, and health care costs)
  - To identify the most appropriate isotope to deliver the treatment.

Conlusion: Anticipated Outcomes

- Comparative efficacy and toxicity data vs the standard of care (docetaxel)
- Valuable information about the benefits of personalized dosimetry
- Set the stage for future Targeted Radionuclide Therapy stage 3 studies on RLT in mCRPC.
- It will also prepare a broader community to conduct large scale clinical trials.

Phase I/II study of ^{225}Ac-PSMA

- Study to determine tolerated dose and establish safety
- Initial dose escalated stepwise until tolerance is established
- Once optimal dose established, confirm with larger number of patients
- Will provide access to potent ^{225}Ac in Canada
- To be determined:
  - Choice of carrier molecule
  - Implementation GMP production
  - Determination of purity of ^{225}Ac supply



68Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting 177Lu-PSMA-617 presented progression (B).

Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

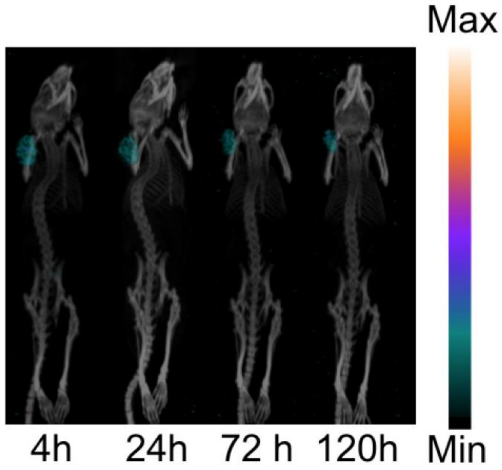
JNM The Journal of NUCLEAR MEDICINE

Timelines

- Vision trial – accrual open in several countries including Canada
- PLUDO trial – currently working with Canadian Clinical Trial Group to implement across Canada – target June 2019
- Phase I/II ^{225}Ac trial
  - Depends on compound selection
  - GMP manufacturing progress
  - Target early 2020

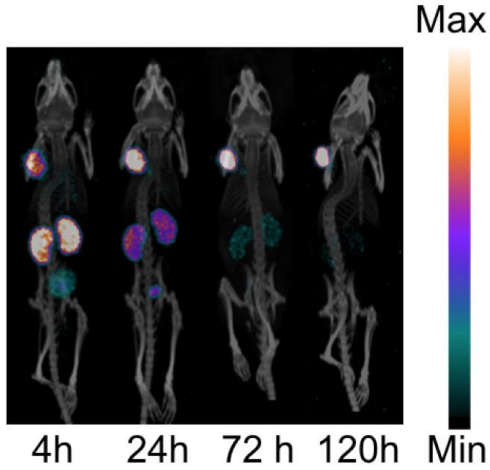
Progress in the lab

^{177}Lu-PSMA-617



LNCaP Tumor uptake:
4 h: 14.5 ± 1.83 %ID/g
24 h: 10.9 ± 3.30 %ID/g
72 h: 7.80 ± 3.69 %ID/g
120 h: 7.91 ± 2.82 %ID/g

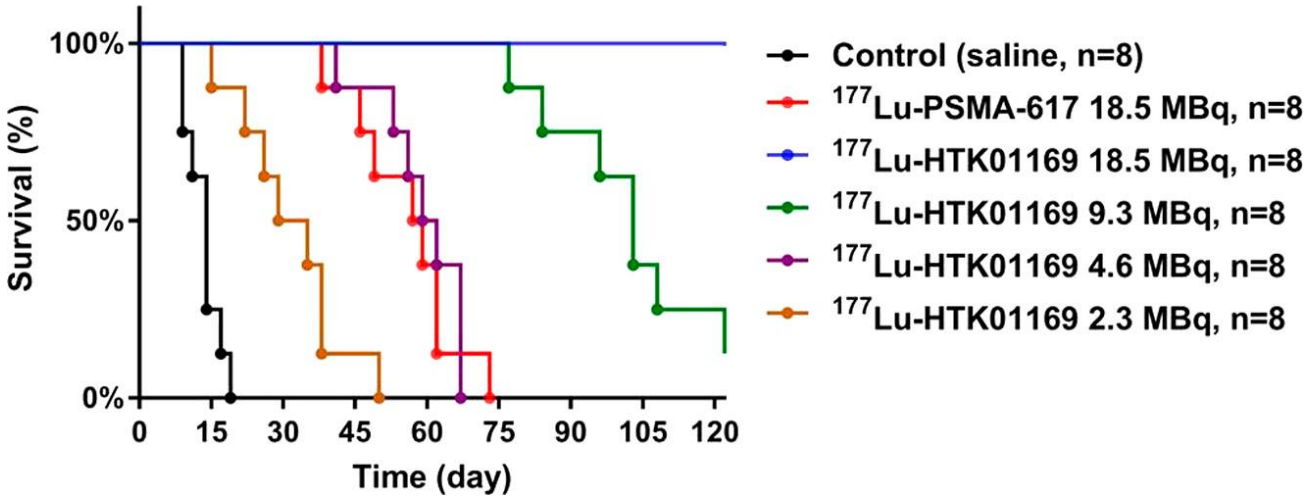
^{177}Lu-HTK01169



LNCaP Tumor uptake:
4 h: 27.2 ± 5.56 %ID/g
24 h: 55.9 ± 12.5 %ID/g
72 h: 53.6 ± 8.06 %ID/g
120 h: 56.4 ± 13.2 %ID/g

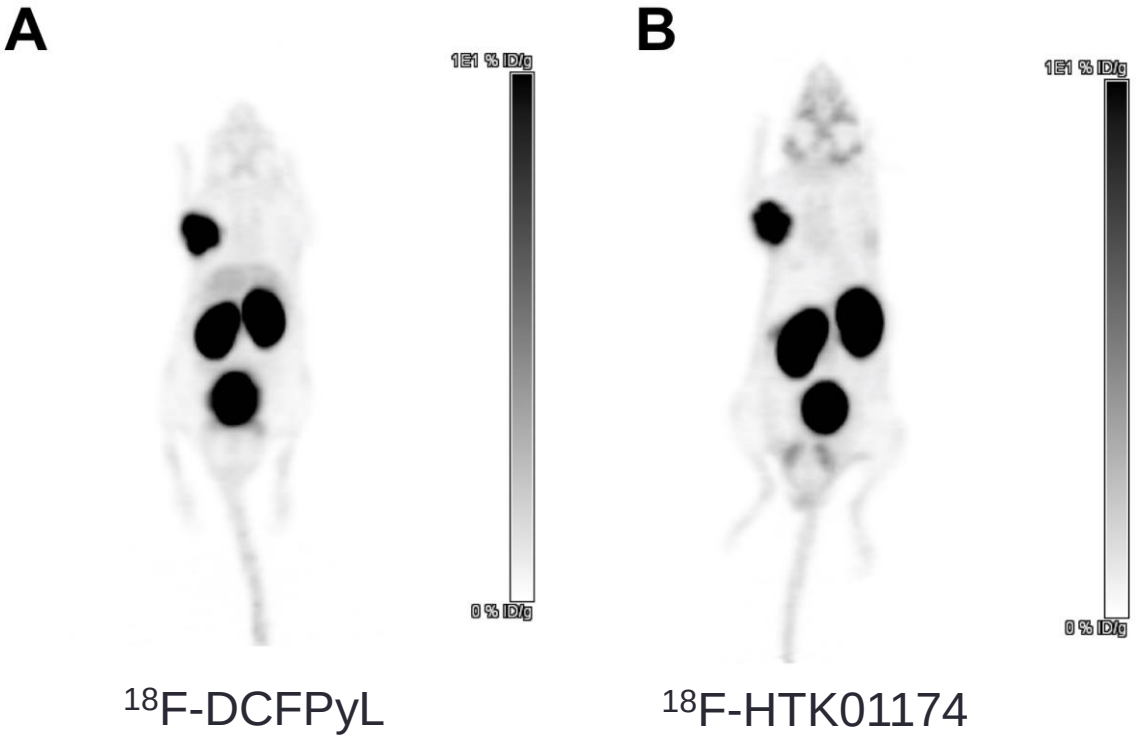
Kuo HT, Merkens H, Zhang Z, Uribe CF, Lau J, Zhang CC, Colpo N, Lin KS, Bénard F.
Mol. Pharmaceutics 15, 5183-5191. DOI: 10.1021/acs.molpharmaceut.8b00720

Improved Therapeutic Compounds



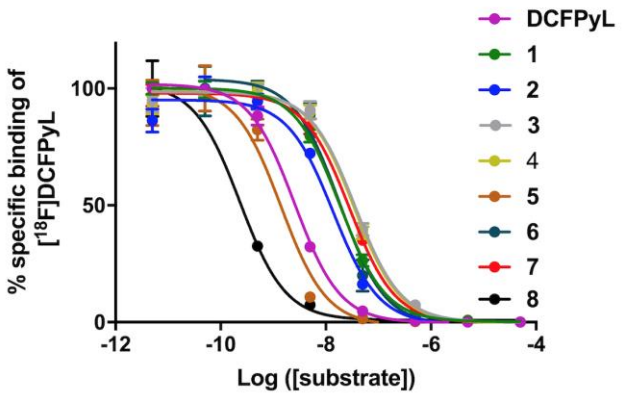
Kuo HT, Merkens H, Zhang Z, Uribe CF, Lau J, Zhang CC, Colpo N, Lin KS, Bénard F.
Mol. Pharmaceutics 15, 5183-5191. DOI: 10.1021/acs.molpharmaceut.8b00720

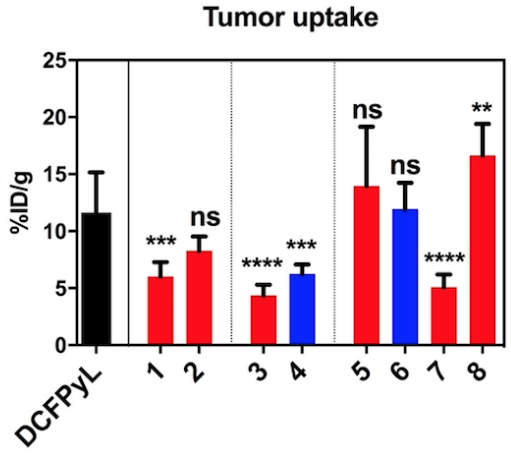
New diagnostic compounds



^{18}F-DCFPyL

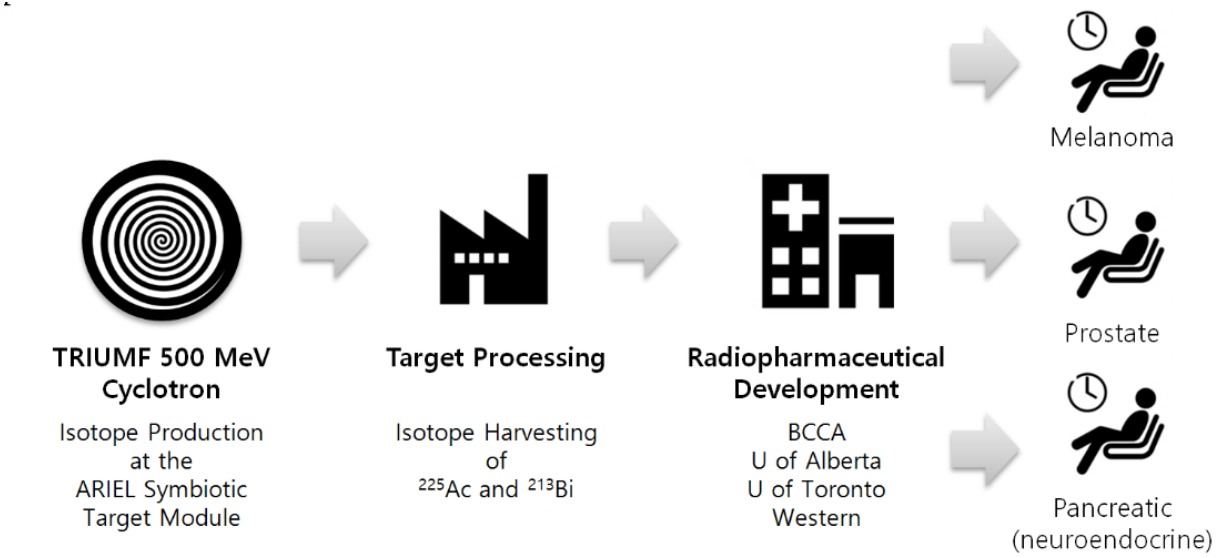
^{18}F-HTK01174



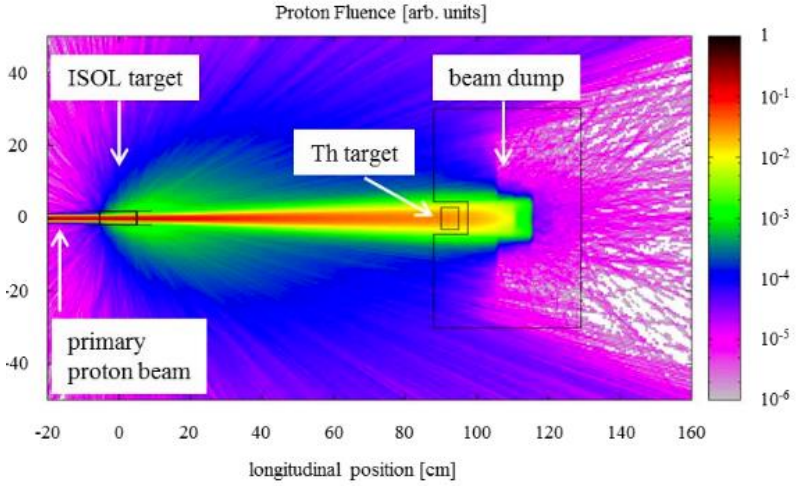


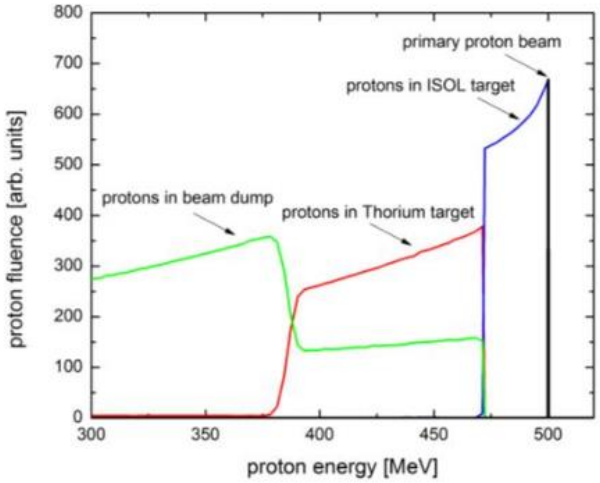
The next frontier: Rare Isotopes for Cancer Therapy

- Newly funded $9.8M addition to TRIUMF's Advanced Rare Isotope Laboratory (ARIEL)



A symbiotic target for alpha emitter production





Potential production yield of 1940 mCi of ^{225}Ac per year
Typical patient dose for PSMA therapy is $\simeq$ 0.2 mCi

Institute for Advanced Medical Isotopes (IAMI)

- New Institute to be built and operated by TRIUMF
- Joint project with BC Cancer and UBC
- Installation of a new 24 MeV cyclotron
- Isotope processing and radiochemistry laboratories
- New BC Cancer laboratory for Radionuclide Therapy manufacturing and development