PROstate-specific membrane antigen DosImetry-Guided endoradiotherapY: A randomized-controlled, single-blind, pilot study of personalized vs. fixed-activity ^{177}Lu-PSMA-617 radiopharmaceutical therapy (PRODIGY-2)

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1. Background and Rationale

Radiopharmaceutical therapy (RPT; a.k.a. radioligand therapy, RLT) directed against prostate-specific membrane antigen (PSMA, a surface protein found on cells of prostate and other cancers) using ^{177}Lu-PSMA-617 has shown to prolong overall survival (OS) and radiographic progression-free survival (PFS) vs. best standard of care in patients with metastatic castrate-resistant prostate cancer (mCRPC) in the VISION phase 3 trial, i.e. the pivotal study that led to the FDA and Health Canada approval of ^{177}Lu-PSMA-617 (Pluvicto®, Novartis).[1] TheraP, a phase 2 Australian trial, also showed increased biochemical response rate (prostate-specific antigen – PSA – decrease by 50%, or PSA50) vs. cabazitaxel chemotherapy.[2] The PSMAfore study showed that, in chemotherapy-naïve mCRPC patients, ^{177}Lu-PSMA-617 prolonged PFS vs. a change in androgen-receptor pathway inhibitor (ARPI).[3] ^{177}Lu-PSMA-617 is well tolerated with serious (grade 3-4) toxicity rates of less than 10%. While promising, these trials were conducted with the conventional fixed-activity approach (e.g. 6 cycles of 7.4 GBq in the VISION and PSMAfore trials), where all patients received the same administered activity, regardless of how the radiopharmaceutical distributes and clears from their body, which are determinants absorbed dose to tissues – dosimetry – that can easily be assessed using quantitative single-photon computed emission tomography (SPECT). It is well known that for a given injected activity, the absorbed doses to healthy organs (in particular to the critical organs: kidneys and salivary glands because of their high uptake, and bone marrow because of its high radiosensitivity) will vary by one order of magnitude or more among patients, and ^{177}Lu-PSMA-617 is no exception.[4] The good tolerance, combined with the high interpatient variability in absorbed dose per administered activity, implies that most patients are undertreated from a dosimetry perspective, i.e. that their body could tolerate a larger activity and consequent larger tumor dose, thus maximizing the likelihood of favorable outcomes without added toxicity. Higher response rates and longer PFS, and perhaps OS, could be hoped for if treatment was optimized for each patient individually, i.e., activity tailored to deliver a standardized absorbed dose to critical organs. Conversely, escalating a fixed activity administered to all patients to achieve tumor dose escalation would inevitably result in increasing rates of serious hematological and potentially renal toxicities.

Besides, the current absorbed dose thresholds for toxicity are derived from external beam radiotherapy (e.g. 23 Gy to the kidney), while it appears that the latter are probably too conservative in the context of radiopharmaceutical therapy.[5] The ^{177}Lu-PSMA-617 regime of 6 cycles of 7.4 GBq every 6 weeks yields a mean population renal cumulative absorbed dose of approximately 19 Gy.[6] There is thus also rationale to explore higher absorbed dose regimes (e.g. up to 40 Gy to the kidney) in a patient population with an otherwise limited prognosis (i.e. median OS was 15.3 mo. in the VISION trial, and 24 mo. in PSMAfore), considering the currently rare incidence of serious renal toxicity (<1%) and the fact that such renal toxicity would be expected to develop over few years (i.e. over a longer period than the cancer prognosis). On the other hand, subacute hematological toxicity is more commonly seen but is generally reversible. Bone marrow dosimetry-based prescription could potentially help to prevent it but, at present, bone marrow dosimetry remains challenging to perform and is less robust than the dosimetry of target organs such as the kidney. In addition, mild/subacute hematological toxicity (e.g.

thrombocytopenia) may act as a convenient "biological dosimeter" to tailor further cycles. Also, late hematological complications such as myelodysplastic syndrome and acute myeloid leukemia can theoretically affect patients a few years later but have seldom been observed with ^{177}Lu-PSMA RPT, probably because of the otherwise limited prognosis of mCPRC patients.

Noteworthily, we observed a correlation between renal and bone marrow absorbed dose in the setting of another ^{177}Lu-based RPT for neuroendocrine tumor, suggesting that prescribing the administered activity based on renal dosimetry may contribute to limit bone marrow dose and subacute hematological toxicity.[7] This could also apply to ^{177}Lu-PSMA. Finally, salivary glands are another critical organ, although not considered vital, and mild xerostomia is common. If salivary glands absorbed dose would be correlated to renal dose to some extent, it is possible that a renal dosimetry-based personalized regime would also limit salivary gland irradiation and side effects.

We hypothesize that personalizing administered activity of ^{177}Lu-PSMA by prescribing a standardized renal absorbed dose would allow to safely increase administered activity and thus tumor absorbed dose in most patients as compared with the fixed-activity empiric regime. This would in turn result in better therapeutic outcomes without adding toxicity. In a stepwise approach before embarking on a phase 2 or 3 randomized trial comparing the efficacy of personalized vs. fixed-activity regimes of ^{177}Lu-PSMA-617, we are proposing a pilot study to assess the feasibility and safety of dosimetry-based ^{177}Lu-PSMA-617.

2. Objectives and Endpoints

2.1. Primary Objectives and Endpoints

Primary objectives	**Primary Endpoints**
1. To compare administered activity between renal dosimetry-based personalized and fixed-activity regimes of ^{177}Lu-PSMA-617 in mCRPC patients	1. Cumulative administered activity comparison: met if ≥ 20/30 participants of Arm A receive either: • a cumulative activity that is larger than the average cumulative activity in Arm B • an activity per cycle that is larger than the average activity per cycle in Arm B
2. To assess the rate of subacute adverse events of special interest (AESIs), in particular subacute renal and hematological toxicity of the personalized regime, as well as that of the fixed-activity regime	2. Safety: met if ≤ 6/30 participants of a given arm experience one or more of the following subacute AESIs with onset ≤ 6 weeks after a ^{177}Lu-PSMA-617 administration: • treatment-related grade 3-4 thrombopenia persisting more than 12 weeks • treatment-related grade 3-4 neutropenia persisting more than 12 weeks

	• treatment-related creatinine elevation to >2x baseline and >ULN (upper limit of normal) persisting more than 12 weeks • treatment-related grade 4 febrile neutropenia • treatment-related grade 4 non-hematological toxicity

2.2. Secondary Objectives and Endpoints

Secondary objectives	**Secondary endpoints**
1. To assess the efficacy of the personalized regime, as well as the that of the fixed-activity regime in the same population, in particular the PSA50 biochemical response rate	1. Efficacy endpoints: • Best biochemical response rate (PSA50, i.e. <50% PSA decline, and other rates such as PSA90, etc.) up to 12 mo. or initiation of another anti-cancer treatment (except palliative radiotherapy to a minority of the tumor burden) • PCWG3 PSA progression-free survival (PFS; time to progression or death: time to increase in PSA of 25% above nadir and >2ng/mL confirmed 3 weeks later) • Best radiological response, overall response rate (ORR) and disease control rate (DCR), based on live investigator's assessment of scheduled and ad hoc conventional (CT, MRI, bone scan), ^{177}Lu-SPECT/CT, and PET/CT imaging up to 12 mo. or initiation of another anti-cancer treatment (except palliative radiotherapy to a minority of the tumor burden) • Radiological PFS (rPFS) as per investigator live assessment of all imaging • Investigator-assessed clinical PFS • Investigator-assessed overall PFS (i.e. earliest clinical, radiological or biochemical progression) • RECIST/PCWG3-based best radiological response, ORR and DCR based on conventional imaging only up to 12 mo. or initiation of another anti-cancer treatment (except palliative radiotherapy to a minority of the tumor burden) • RECIST/PCWG3-based rPFS based on conventional imaging only • Time to first skeletal event • Overall survival (OS) • Metabolic response on FDG-PET/CT at 3 mo. • Molecular response on PSMA-QSPECT/CT during treatment • Molecular response on PSMA-PET/CT at end of treatment (EOT)

2. To assess the safety of both regimes of ^{177}Lu-PSMA-617, including delayed AESIs such as renal impairment and secondary hematological malignancies	2. Safety endpoints: • Symptomatic AEs until EOT visit, or progression, or initiation of another cancer treatment (except palliative radiotherapy), whichever is earliest • Laboratory AEs until progression, initiation of another cancer treatment (except palliative radiotherapy), or study termination, whichever is earliest • Delayed AESIs until death or study termination, whichever is earliest: ○ renal impairment ○ secondary hematological malignancies
3. To assess on patient-related outcomes measures (PROMs), including salivary gland toxicity	3. PROM endpoints: • Salivary gland function (variation from baseline) evaluated with MSGS questionnaire • Quality of life PROMs (variation from baseline) evaluated with EQ-5D-5L, FACT-P and BPI-SF questionnaires

2.3. Exploratory Objectives and Endpoints

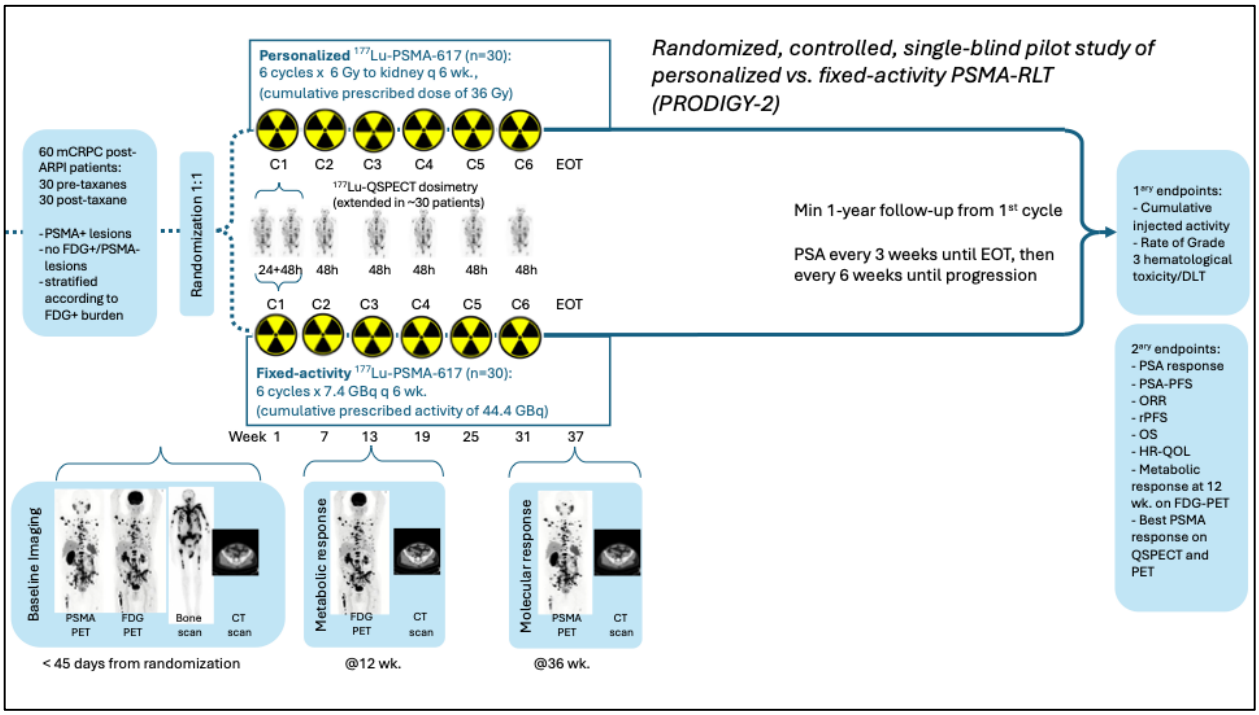
Exploratory objectives	**Exploratory endpoints**
1. To develop practical dosimetry methods for personalized ^{177}Lu-PSMA;	1. Percent deviation of dosimetry estimates derived from the simplified dosimetry protocol from those with additional timepoints
2. To develop molecular (PSMA) and metabolic (FDG) PET imaging response criteria;	2. Percent variation of PSMA SPECT/CT and PET/CT, and FDG-PET/CT-derived parameters (e.g. SUV, MTV, TLA, TLF) from baseline, and correlation with biochemical and conventional imaging response criteria
3. To assess tumor dose-response and healthy tissue dose-toxicity relationships;	3. Correlations between tumor or organ/surrogate absorbed dose and efficacy or safety endpoints, respectively
4. To explore clinical, imaging and biological biomarkers (including artificial intelligence (AI)-generated ones) of potential predictive or prognostic values in the context of ^{177}Lu-PSMA RPT;	4. Appropriate group comparisons, variable correlations and/or multivariate analyses will be applied to derive biomarkers of potential predictive (e.g. of dosimetry, efficacy, or toxicity) or prognostic values, among: • Clinical features • Imaging features (radiomics) • Biological features (e.g. collected results from pathology and labs performed as standard of care, or on biobank samples, for those participants also participating in a cancer-related biobank accessible to the investigators)

5. To improve and automate quantitative SPECT imaging and dosimetry workflows (including use of AI techniques);	5. Comparison of novel reconstructions, segmentations and dosimetry estimates generated using advanced techniques (incl. AI) with conventional ones
6. To enable the use of the imaging and clinical data collected through this study for secondary research and development, through an imaging and data bank.	6. Creation of an imaging and data bank through a separate consent

3. Study design, number of participants and duration

- This study is a single-center, single-blind, pilot randomized trial of personalized vs. fixed-activity ^{177}Lu- PSMA-617 in mCRPC patients having received at least one ARPI and who are progressing biochemically (Fig. 1)
- **60 eligible participants** will be randomized 1:1 in blocks of 4 participants, with stratification for significant FDG-positive metabolic tumor volume (MTV; < 200 mL vs. ≥ 200 mL) [8], to:
    - **Arm A: Personalized ^{177}Lu-PSMA-617 activity** for a prescribed renal absorbed dose of 6 Gy per cycle, up to 6 cycles every 6 weeks
    - **Arm B: Fixed ^{177}Lu-PSMA-617 activity** of 7.4 GBq per cycle, up to 6 cycles every 6 weeks
- Participants will be subgrouped according to their chemotherapy exposure status in mCRPC (chemo-naïve or post-taxane for mCRPC), with a target of 30 (and no less than 24) participants per subgroup.
- Accrual is expected over a period of two years.
- Minimum follow-up of participants is one year, for an anticipated **minimum study duration of three (3) years**. Follow-up could be prolonged up to five years after the last participant accrual to capture additional PFS and OS events as well as delayed AESIs.
- Participants withdrawn for reasons other than progression, clinical deterioration or toxicity will be replaced if possible.

Fig. 1. Study Schema



4. Eligibility

4.1. Inclusion criteria

1. Patient aged ≥18 years with metastatic adenocarcinoma of the prostate, defined by documented histopathology of prostate adenocarcinoma;
2. Castration-resistant prostate cancer, as defined as disease progressing despite castration by orchiectomy or ongoing androgen deprivation therapy;
3. Progressive mCRPC with rising PSA level, defined by PCWG3 criteria (sequence of two rising values above a baseline at a minimum of 1-week intervals, with serum testosterone level ≤ 1.7 nmol/dL);
4. PSA ≥5 ng/mL ;
5. Prior treatment with at least one ARPI;
6. PSMA-expressing cancer, with significant PSMA expression defined as SUV_{peak} in at least one lesion that is superior to SUV_{mean} of the liver on PSMA-PET (^{68}Ga-PSMA-11 or ^{18}F-DCFPyL), within 45 days prior to randomization;
7. ECOG Performance status 0 to 2;
8. Calculated eGFR (by CKD-EPI formula) ≥ 45 mL/min/1.73m^2;
9. Albumin ≥ 25 g/L;
10. Platelets ≥ 100x10^9/L;
11. Neutrophils ≥ 1.5x10^9/L;

12. Hemoglobin ≥ 90 g/L without transfusion in the past 4 weeks;
13. Signed, written informed consent

4.2. Exclusion criteria

1. PSMA-PET "superscan" (i.e. extensive/diffuse PSMA-positive bone involvement);
2. Site(s) of disease that are FDG-positive, defined as SUV_{peak} in at least one lesion that is superior to twice (2x) SUV_{mean} of the liver, and PSMA-negative (as above), within 45 days prior to randomization;
3. Prior treatment with more than one line of chemotherapy for mCRPC;
4. Prior radiopharmaceutical therapy;
5. Known CNS metastasis unless they are deemed to be non-progressive, asymptomatic and off corticosteroid therapy for at least four weeks, as per investigator's assessment
6. Active malignancy other than prostate cancer;
7. Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception;
8. Any other condition, diagnosis or finding that may in the investigator's opinion interfere with trial conduct

5. Baseline assessment

- Clinical information from pre-enrolment consultation/visits and medical record:
  - History of the prostate cancer
  - Past medical history
  - Medication
  - Performance status
  - Measured weight and height within 45 days from randomization
- Imaging (reports and DICOM images):
  - PSMA-PET and FDG-PET (within 45 days from randomization)
  - Conventional imaging, including CT and/or MRI, bone scan (within 45 days from randomization)
- Prostate cancer-related pathology reports
- Lab results within 45 days of randomization, for eligibility, to be repeated within 4 days before first cycle, as baseline:
  - Hematology (blood counts)
  - Biochemistry (creatinine, LDH, albumin, alkaline phosphatase, PSA including serial values to document progression)
  - Other labs relevant to the participant's cancer disease
- PROMs within 4 days before first cycle:
  - Multidisciplinary Salivary Gland Society (MSGS) Questionnaire[9]
  - EQ-5D-5L
  - Brief Pain Inventory – Short Form (BPI-SF)
  - Functional Assessment of Cancer Therapy – Prostate (FACT-P)

6. Intervention

- Up to 6 induction cycles of ^{177}Lu-PSMA-617 (provided by Novartis) will be administered with a target interval of 6 weeks, at the following administered activities:
    - Arm A (Personalized):
        - First cycle: 0.07 x Body-surface area (BSA, Mosteller formula) x eGRF (CKD-EPI formula) GBq
        - Cycles 2-6: 6 Gy divided by prior cycle renal Gy/GBq
    - Arm B (Fixed-activity):
        - 7.4 GBq per cycle
- Interval up to 12 weeks is allowed to recover from subacute toxicity. Efforts will be made to limit delays due to logistical reasons.
- Induction cycles will be stopped upon:
    - Unequivocal progression (imaging, PSA, and/or clinical) as per the investigator's assessment, considering the following:
        - Treatment continuation is encouraged until at least PCWG3 PSA progression, i.e. an increase in PSA greater than 25% and >2 ng/ml above nadir, confirmed by progression at 2 timepoints at least 3 weeks apart.
        - In the case of isolated PSA progression (i.e. without imaging or clinical progression), documentation of progression by imaging (conventional imaging and/or next cycle ^{177}Lu-SPECT/CT) is encouraged before initiation of another treatment (except palliative radiotherapy to a minority of the tumor burden).
    - Any of the following subacute AESIs with onset within 6 weeks after any administration of ^{177}Lu-PSMA-617:
        - treatment-related grade 3-4 thrombopenia persisting more than 12 weeks
        - treatment-related grade 3-4 neutropenia persisting more than 12 weeks
        - treatment-related creatinine elevation to >2x baseline and >ULN persisting more than 12 weeks
        - treatment-related grade 4 non-hematological toxicity
        - treatment-related grade 4 febrile neutropenia
- After grade "1b" thrombopenia (defined as platelets decreasing to 75-100x10^9/L), recovered or not, the participant will receive, at the subsequent cycle, the lowest of:
    - Last cycle administered activity (Arm A and B)
    - Dosimetry-based prescription (Arm A only)
- After treatment-related grade 3-4 neutropenia or thrombopenia, or creatinine elevation to >2x baseline and >ULN that recovered to a lower grade within 12 weeks, or grade 2 thrombopenia, the participant will receive, at the subsequent cycle, the lowest of:
    - Last cycle administered activity reduced by 33% (Arm A and B)
    - Dosimetry-based prescription reduced by 33% (Arm A only)
- If there is a complete response (i.e. PSA undetectable AND no detectable PSMA-avid disease on ^{177}Lu-PSMA-SPECT/CT) during the induction course, the remaining induction

cycles may be administered or not, as per assessment of risks vs. benefits by the investigator and as per participant's preference. The remaining cycles can be administered after confirmed PSA progression or unequivocal imaging progression (as per standard of care and assessed by investigator).

7. Dosimetry

- The final simplified dosimetry protocol is expected to consist in 2 or 3-bed quantitative SPECT/CT (including at least parotids to ischium) at 2 timepoints (24±8h and 48±8h) after the first cycle and at one timepoint (48±8h) at subsequent cycles. Exceptionally, the 24h or the 48h timepoint can be substituted by a 72±8h timepoint, and this would be noted as a minor deviation.
- The primary renal dosimetry assessment methods are as follows: activity concentration (Bq/cc) is sampled using a 2-cm sphere volume of interest (VOI) centered on SUV_{peak} 1-cc sphere location over combined renal parenchyma of both kidneys. Effective half-life derived from monoexponential fit over the two timepoint of first cycle will be propagated to the single timepoint data of subsequent cycles. The activity concentration dose factor will be 86 mGy-cc/MBq-h.[10] The other dosimetry measures are observational/exploratory and not detailed here.
- To optimize and validate the simplified dosimetry protocol, in up to 30 participants from any arm, a 3-bed quantitative SPECT/CT (15 s/frame; 96 frames) and rapid WB planar (60 cm/min) will be performed at:
    - Cycle 1: 5 timepoints (mono or bi-exponential fits)
        - 1±0.5h (pre-void), 24±8h, 48±8h, 72±8h and 88-176 h (SPECT increased to 20 s/frame for the latter)
    - Cycle 2: 3 timepoints (mono-exponential fit)
        - 24±8h, 48±8h, 72±8h
    - Cycle 3: 2 timepoints (mono-exponential fit)
        - 24±8h, 48±8h
    - Cycle 4 to 6: 1 timepoint
        - 48±8h
- The timing and number of scans could be revised/optimized based on ongoing analyses. If medically advised as per investigator's assessment, the imaging schedule may be modified in patients with a particular condition (e.g. renal impairment) to obtain more accurate dosimetry estimates than it is possible with the simplified protocol.
- All DICOM images will be collected.
- Correlation to blood sampling-based dosimetry could be performed in up to 30 participants to validate image-based bone marrow dosimetry methods (up to 10 times 10mL - 5mL flush plus 5mL sample - of blood from i.v. catheter in the opposite arm than that for the treatment administration).
- Up to 48h urine sampling may be used in up to 30 participants to validate whole-body retention.

- Participants will be informed of the planned imaging schedule, and if applicable of blood and/or urine sampling schedule in the consent form. Additional imaging sessions or blood/urine sampling not initially planned and not medically required will be optional for the participant.
- Arm A only: Exceptionally, if dosimetry cannot be performed or yields inconsistent or doubtful results, the investigator may elect to use the data from the last valid dosimetry study, or from BSA and eGFR calculation to prescribe activity. These cases may be excluded from the per-protocol analyses.

8. Follow-up

- End-of-treatment (EOT) visit will be performed at 6 (+/-1) weeks after last cycle, or as soon as possible after progression and before initiation of another anti-cancer treatment
- Long-term follow-up (LTFU) visits consist in review of medical record, a medical visit or phone call to the participant or relative, or discussion/correspondence with other physician(s) involved in the care of the participant, and will be performed at least once every 12 (+/-2) weeks until progression, or initiation of another anti-cancer treatment
- Thereafter, periodic review of the record and/or call to the participant/relative or other physician(s) involved in the care of the participant will be performed to determine the date and cause of death, as well as the occurrence of SAEs of particular interest.
- Clinical information collected from follow-up visits and medical record:
    - Evolution of prostate cancer, including other treatments received
    - Evolution or emergence of other medical conditions
    - Performance status
    - Medication
- Imaging (reports and DICOM images collected):
    - FDG-PET and CT scan at 12 weeks (+/- 1 week)
    - PSMA-PET and CT scan at EOT
    - As per standard of care in all participants until definite progression (including CT, MRI, PET, nuclear medicine)
- Labs:
    - Blood counts, creatinine, PSA every 21 days (+/- 4 days, or within 4 days before the next cycle) until one year or progression, and every 6 weeks (+/- 1 week) until progression. The investigator may prescribe additional ad hoc testing for following-up toxicities.
    - All relevant labs as per standard of care may be collected to assess efficacy or toxicity until death.
- AEs:
    - Symptomatic AEs: At each treatment and EOT visits, A research nurse or an investigator/physician will collect symptomatic AEs and review medical record for AEs

    - Treatment-related laboratory AEs: Laboratory (blood counts and creatinine) until progression or initiation of another anti-cancer treatment, whichever is earliest
    - SAEs of special interest (development of secondary hematological malignancies or delayed renal impairment): during long-term follow-up, through periodic medical record review and/or contact of participant or relative, as for survival.
- PROMs within one week before cycle 4 and at EOT visit: EQ-5D-5L, FACT-P, BPI-SF, MSGS.

Table 1. Schedule of activities

	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		EOT	LTFU
Study week	**-4**	**1 (BL)**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**31**	**34**	**37**	**53 & q 12 weeks**
Consent	X														
Eligibility	X														
Demographics	X														
Medical history	X														
Prior meds	X														
Bone scan	X														
CT scan (or MRI)	X					X								X	
FDG-PET	X					X									
PSMA-PET	X													X	
Weight and Height	X	X		X		X		X		X		X		X	
Cancer-related meds	X	X		X		X		X		X		X		X	X*
ECOG and KPS	X	X		X		X		X		X		X		X	X*
Randomization	X														
AEs		X		X		X		X		X		X		X	
Delayed AESIs														X	X
Lu-PSMA-617 infusion		X		X		X		X		X		X			
SPECT/CT imaging		X		X		X		X		X		X			
Blood and/or urine activity		(X)		(X)		(X)		(X)		(X)		(X)			
PSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (q 6 wk.)*
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (q 6 wk.)*
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X (q 6 wk.)*
Questionnaires:															
EQ-5D-5L		X						X						X	
FACT-P		X						X						X	
BPI-SF		X						X						X	
MSGS		X						X						X	
Skeletal events		X		X		X		X		X		X		X	X*
Progression		X		X		X		X		X		X		X	X*
Survival														X	X

* Until progression

Imaging procedures described above are considered standard-of-care, except:

- Follow-up FDG at week 13 and PSMA-PET at EOT
- SPECT/CT in excess of one per cycle (see Section 7)

9. Statistical Plan

9.1. Sample size

The primary objectives are proportions with target "Go/No-Go" thresholds justified by experience and clinically relevant expectations. With a sample size of 30 patients per arm, this pilot study is designed to achieve the desired outcomes for both primary endpoints:

- For the first primary endpoint, a sample size of 30 per arm will yield a two-sided 95% confidence interval with a width equal to 0.34 that the observed proportion of at least 67% of Arm A participants with a cumulative or per cycle administered activity higher than the average of Arm B, will not have a lower confidence boundary below 50%.
- For the second primary endpoint, a sample size of 30 per arm will produce a two-sided 95% confidence level with a width of 0.29 when the observed sample proportion of subacute adverse events of special interest (AESIs) is 20%, ensuring that the upper confidence boundary does not exceed 34%.

9.2. Statistical analyses

The full sample and each study arm will be described using the mean ± standard deviation, 95% confidence intervals, median, interquartile range, and simple range for continuous variables, as well as frequency and percentage for categorical variables. The proportion of participants in Arm A who received a cumulative activity exceeding the average activity in Arm B (cumulative and per cycle) will be estimated, along with the incidence of subacute AESIs, both with their 95% confidence intervals. Next, total administered activity per patient of ^{177}Lu-PSMA as well as the average administered activity per cycle and per patient between the two arms will be compared using the Student T-Test or the Wilcoxon-Mann-Whitney test, as appropriate. A generalized estimating equations linear regression model will be applied to compare the average administered activity per cycle to account for correlation due to repeated measures. Chi-Square tests and generalized linear models will be used to evaluate the secondary objectives. Finally, survival analyses, including Cox proportional hazards models and Kaplan-Meier estimates, will assess PFS and OS outcomes. All statistical analyses will be performed using SAS Statistical Software v.9.4 (SAS Institute, Cary, NC, USA) with a two-sided significance level of $p < 0.05$.

10. Adverse events

AEs will be collected primarily by a research nurse on a form (source document) and eCRF, graded according to CTCEA 5.0, and assess for relatedness by an investigator. Suspected unexpected serious adverse reactions (SUSARs) will be reported to the REB, to Health Canada, and submitted for review to the DSMB. Serious adverse reaction will be categorized as expected or unexpected based on data from the ^{177}Lu-PSMA-617 monograph (Pluvicto®, Novartis).

11. Monitoring

A monitoring plan will be implemented, and monitoring will be performed by a monitor independent from the research team for this study.

12. Data and safety monitoring board (DSMB)

An independent data and safety monitoring board (DSMB) of at least 3 experts with multidisciplinary and relevant expertise will be constituted and meet:

- After 6 participants from Arm A have been treated with at one or two cycles and followed up for at least 12 weeks;
- Then yearly;
- Ad hoc if more than 33% of participants experience one or more pre specified subacute AESI;
- Ad hoc if more than 15% or participants experience a particular treatment-related SEA other than a pre specified subacute AESI;
- Ad hoc if a SUSAR occurs;
- Ad hoc if a protocol amendment that would result in personalized regime intensification is considered

The research team will present a summary of efficacy and toxicity data and, if relevant, will detail cases of particular interest. The DSMB will then deliberate and advise on the continuation, termination or modification of the trial.

13. Data management

The data will be collected by the research team in a secured REDCap database. Source documents will be kept in lockers. A secured electronic file or software will be used for maintaining the participant code list.

Original imaging files will be kept on nuclear medicine imaging servers within the clinical network of CHU de Québec-Université Laval. De-identified version of the clinical and imaging data will be shared in real-time with collaborators at University of British Columbia (Arman Rahmim and Carlos Uribe) who will contribute to the analyses for the secondary and exploratory objectives.

De-identified version of the clinical and imaging data may also be placed on a research data repository approved by the CHU de Québec's Research Ethics Board, to constitute an imaging and data bank (for participants providing a separate consent) and would only be accessible according to the terms of a management framework and data access/transfer agreement if applicable. The principal investigator will be responsible for data sharing with third parties.

If secondary research involves linking the study data with other data not collected in this study, a Research Ethics Board approval will be necessary.

All records related to the study will otherwise be kept securely according to institutional policy for at least 15 years after study termination.

The identity of the participants will only be known to the research team and internal collaborators. All data will be de-identified before sharing with external third parties (unless, if required, with regulatory authorities), as well as in any publication.

Secondary use of data is defined as “Broad use”, e.g. that data may be used in future research and development within or beyond the general area of research of the current study. It can include sharing the de-identified data with industrial partners for the development of commercial products and their promotion.

14. References

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