# Population pharmacokinetics of [$^{177}$Lu]Lu-PSMA-617 combined with EBRT and ADT in treatment naïve patients: differences in tumor uptake and cycle-dependent-effects

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## Introduction

- [$^{177}$Lu]Lu-PSMA is an approved radioligand therapy that improves survival in metastatic castration resistant prostate cancer.
- PROQURE-I (phase I) evaluated [$^{177}$Lu]Lu-PSMA-617 in **treatment-naïve early-stage prostate cancer patients** combined with external beam radiotherapy (EBRT) + androgen deprivation therapy (ADT)[1].
- Pharmacokinetics show high variability, especially in tumor exposure. In the metastatic monotherapy setting, population PK models partly explained this with **treatment cycle** and **tumor volume** effects[2,3] .

## Aim

**To quantify the distribution and variability of [$^{177}$Lu]Lu-PSMA-617 and assess whether covariates identified in metastatic monotherapy setting explain tumor exposure variability in early-stage prostate cancer patients.**

## Key findings & Conclusion

- Lower tumor uptake vs. metastatic monotherapy → **target-mediated drug disposition**[3].
- Cycle 2 uptake reduced to 58% of cycle 1, likely from **EBRT + ADT**.
  - **Importance of first-cycle activity and treatment timing.**
- Tumor volume effect: 2-fold increase volume → ~2.2-fold increase in $k_{12}$ (122%).
- Nonlinear tumor uptake ($B_{max}$) not identifiable; ≥65 patients needed for adequate power (post-hoc power analysis (SSE), 80% power).

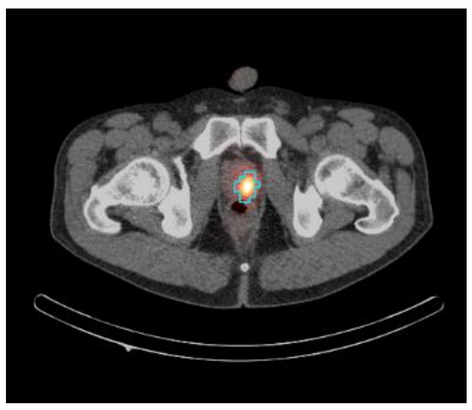
## Methods & Clinical Data

**Table 1.** Patient and study information

| Characteristic | Median [range] |
|---|---|
| Patients (n) | 12 |
| Injected radioactivity (GBq) | 3, 6, 9, 7.4 (2x), |
| Plasma sampling times | 5m, 15m, 30m, 1h-3h, 6h, 24h, 48h, 168h |
| SPECT/CT scan times (h) | 4, 24, 168 |
| Volume of segmented primary tumor (mL) | 11.36 [0.88-35.52] |
| Weight (kg) | 82 [70-98] |
| Age (years) | 64 [56-77] |
| Patients per dose group (n) | |
| 3 GBq | 1 |
| 6 GBq | 1 |
| 7.4 Gbq (2 cycles, 2 week interval) | 5 |
| 9 GBq | 5 |

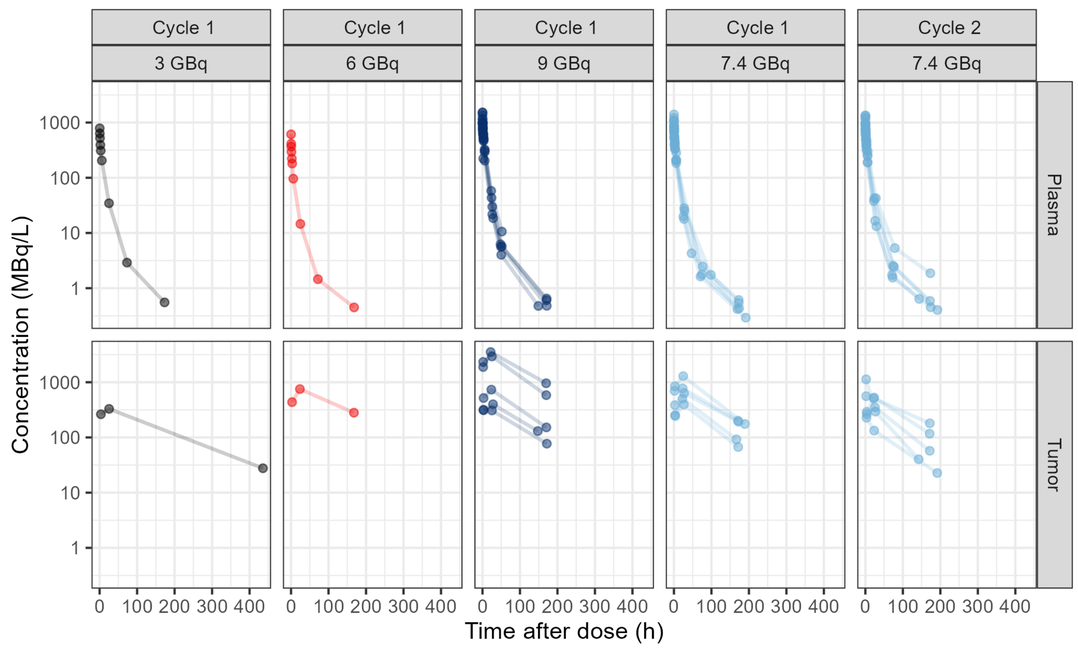
ADT = androgen deprivation therapy, EBRT = external beam radiotherapy. See [1] for additional information regarding the trial protocol

**Figure 1.** Example of semi-automatic tumor segmentation



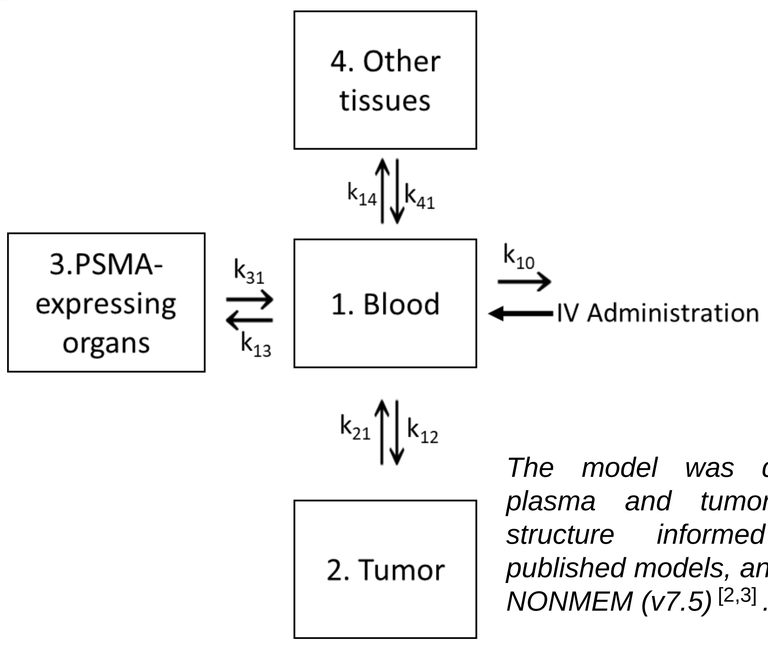
*MIM software (version 7.3.6) was used to acquire volumes (L) and mean uptake (MBq/L) in tumors.*

**Figure 2.** Concentration (MBq/L) time curves




## Model Structure & Parameters

**Figure 3.** Schematic overview of the final population PK model structure




*The model was developed using plasma and tumor data, with a structure informed by previous published models, and implemented in NONMEM (v7.5)* [2,3] *.*

**Table 2.** Estimated parameters of the final population PK model

| Parameter | Estimate (RSE%) | 95% CI |
|---|---|---|
| **Population parameters** | | |
| $k_{10}$ ($h^{-1}$) | 0.266 (5.6%) | 0.235 - 0.294 |
| $k_{12}$ tumor ($h^{-1}$) | 0.000586 (10.5%) | 0.000462 - 0.000710 |
| Cycle effect[b] | 0.576 (20.6%) | 0.355 - 0.823 |
| Tumor volume effect[c] | 1.14 (9.3%) | 0.955 - 1.38 |
| $k_{21}$ tumor ($h^{-1}$) | 0.0122 (7.5%) | 0.0102 - 0.0138 |
| $k_{13}$ PSMA organs ($h^{-1}$) | 0.0219 (3.9%) | 0.0201 - 0.0233 |
| $k_{31}$ PSMA organs ($h^{-1}$) | 0.0170 (5.9%) | 0.0151 - 0.0190 |
| $k_{14}$ other tissues ($h^{-1}$)[a] | 1.05 | |
| $k_{41}$ other tissues ($h^{-1}$)[a] | 0.741 | |
| $V_1$ (L) | 4.93 (3.3%) | 4.64 - 5.26 |
| **Inter-individual variability (CV%)** | | |
| $k_{10}$ | 23.2 (35.0%) | 16.2 - 32.4 |
| $k_{12}$ tumor | 89.4 (35.7%) | 59.6 -139 |
| $k_{14}$ other tissues | 46.4 (45.9%) | 30.5 - 73.4 |
| **Residual unexplained variability (CV%)** | | |
| Proportional error plasma | 16.3 (13.0%) | 14.6 - 18.8 |
| Additive error plasma (MBq/L)[a] | 0.25 | |
| Proportional error tumor | 57.0 (23.9%) | 48.4 - 82.1 |

[a]Fixed parameter, [b]Added as fractional change, [c]Added using a power covariate function, 95% CI and RSE obtained from the sampling importance resampling (SIR). CV% coefficient of variation, $V_1$ central volume of distribution.

## Model Evaluation & Simulations

**Figure 4.** Prediction corrected VPC for blood plasma (**A**) and tumor (**B**)

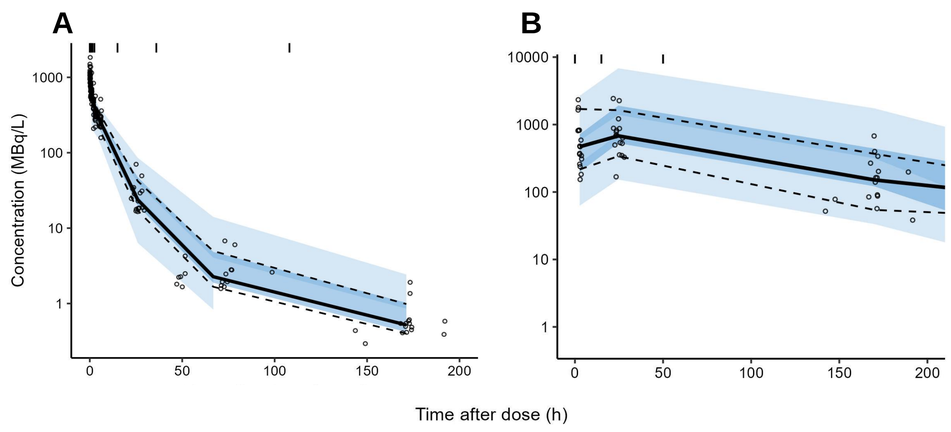
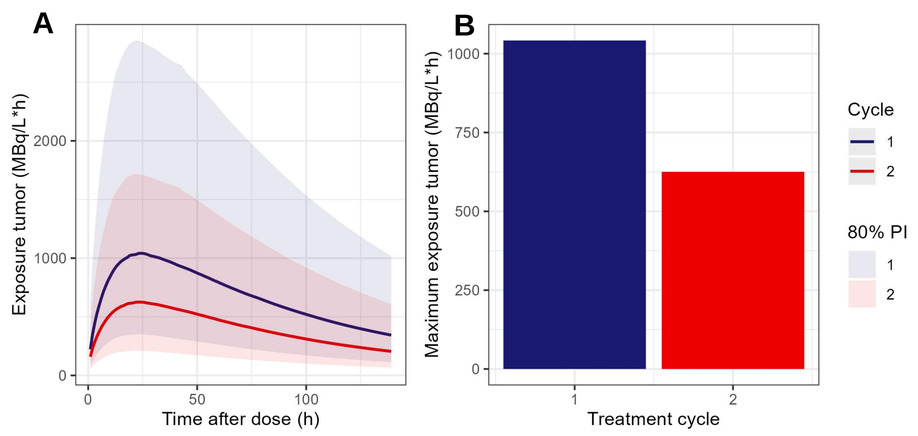



**Figure 5.** Simulation of typical patients (n=1000) receiving 7.4 GBq.
***(A)**. Median and 80% PI, (**B**). Median maximum tumor exposure per cycle*




1. van der Sar, *et al*. Tolerability of concurrent external beam radiotherapy and [177Lu]Lu-PSMA-617 for node-positive prostate cancer in treatment naïve patients, phase I study (PROQURE-I trial). BMC Cancer. 2023.
2. Siebinga H, *et al*. Quantification of biochemical PSA dynamics after radioligand therapy with [177Lu]Lu-PSMA-I&T using a population pharmacokinetic/pharmacodynamic model. EJNMMI Phys. 2024
3. Siebinga H, *et al* Population pharmacokinetic dosimetry model using imaging data to assess variability in pharmacokinetics of 177Lu-PSMA-617 in prostate cancer patients. CPT Pharmacometrics Syst Pharmacol. 2023

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