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Enhanced Therapeutic Response to ^{177}Lu-rhPSMA-10.1 in Pre-clinical Models of Prostate Cancer

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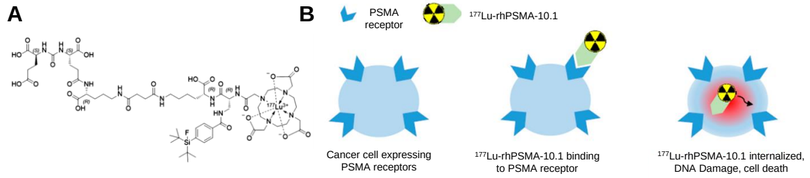
BACKGROUND

- Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) has been shown to extend progression-free and overall survival for men with metastatic castration-resistant prostate cancer (mCRPC).[1]
- We have developed a novel radiohybrid (rh) PSMA radiopharmaceutical for RLT (^{177}Lu-rhPSMA-10.1, Figure 1) with low kidney uptake, rapid blood clearance, and high accumulation in tumors.[2]
- ^{177}Lu-rhPSMA-10.1 has also demonstrated effective suppression of tumor growth *in vivo*,[3] and promising efficacy in a patient with mCRPC.[4]

FIGURE 1. ^{177}Lu-rhPSMA-10.1 (A) and proposed mode of action (B)



OBJECTIVES

- Investigate therapeutic responses to ^{177}Lu-rhPSMA-10.1 in two prostate cancer xenograft models with high and relatively low PSMA expression (LNCaP and 22Rv1, respectively).
- Examine the dose-response relationship of ^{177}Lu-rhPSMA-10.1 in LNCaP xenografts.
- Compare the therapeutic efficacy of ^{177}Lu-rhPSMA-10.1 vs ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T in 22Rv1 xenografts.
- Assess the toxicity of ^{177}Lu-rhPSMA-10.1 based on body weight changes.

METHODS

LNCaP and 22Rv1 PCa xenografts generated in NMRI nude mice
- Subcutaneous inoculation of 5×10^6 LNCaP or 3×10^6 22Rv1 cells per mouse

Study drug administered at baseline (Day 0)
LNCaP mice (n=8 per group):
- Three dose levels of ^{177}Lu-rhPSMA-10.1: 15 MBq, 30 MBq, or 45 MBq

22Rv1 mice (n=8 per group):
- ^{177}Lu-rhPSMA-10.1, ^{177}Lu-PSMA-617, or ^{177}Lu-PSMA-I&T (30 MBq each)

Tumor growth and body weight measurements
- Tumor volume calculated using: 0.52 (length×width^2)
- Every 2 weeks until maximum tumor volume reached (1500 mm^3), or study endpoint (Day 49)

Data analysis
- Relative tumor volume (change from baseline [Day 0]), presented as mean ± SEM.
- Survival of mice was compared across treatments, up to 49 days post-injection
  - Data were analyzed until n=3 per group remained
  - Two-way ANOVA and Kaplan-Meier survival log-rank analyses performed; statistical significance: p≤0.05
- Toxicity assessments: relative body weight (change from baseline [Day 0])

RESULTS

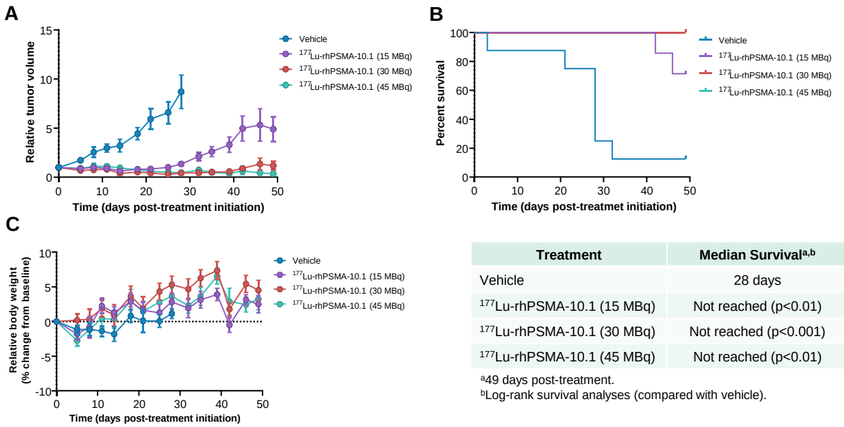
Efficacy of ^{177}Lu-rhPSMA-10.1 in LNCaP xenografts (dose-response)

- ^{177}Lu-rhPSMA-10.1 significantly suppressed tumor growth from Day 11 ($p<0.05$) to Day 32 ($p<0.0001$), Figure 2A, and prolonged survival ($p=0.001$; Figure 2B) at all doses, compared with vehicle.
- Tumor growth was significantly reduced with 30 MBq and 45 MBq vs 15 MBq from Day 35 ($p=0.001$) to Day 49 ($p<0.0001$), suggesting a dose-response effect (Figure 2A).
- Median survival for the vehicle group was 28 days, and was not reached for any of the ^{177}Lu-rhPSMA-10.1 groups by study endpoint (Figure 2B); all mice were still alive in the 30 MBq and 45 MBq groups.
- All ^{177}Lu-rhPSMA-10.1 doses were well-tolerated, with no significant weight loss encountered in any of the treatment groups (Figure 2C).

Efficacy of ^{177}Lu-rhPSMA-10.1 compared with ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T in 22Rv1 xenografts

- ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-617 significantly suppressed tumor growth from Day 18 ($p<0.05$) to Day 35 ($p<0.0001$), Figure 3A, and prolonged survival ($p\leq0.01$; Figure 3B) compared with vehicle, whereas ^{177}Lu-PSMA-I&T inhibited tumor growth from Day 25 ($p<0.05$) to Day 35 ($p<0.0001$), Figure 3A.
- Compared with ^{177}Lu-PSMA-I&T, ^{177}Lu-rhPSMA-10.1 significantly reduced tumor growth from Day 32 ($p<0.05$) to Day 49 ($p<0.0001$), whereas ^{177}Lu-PSMA-617 significantly reduced tumor growth on Day 49 only ($p<0.05$).
- Median survival was 33.5 days for vehicle, 44 days for ^{177}Lu-PSMA-I&T, and not reached for the ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-617 groups (Figure 3B).
- All treatments were well-tolerated, with no significant weight loss observed in any of the treatment groups throughout the study period (Figure 3C).

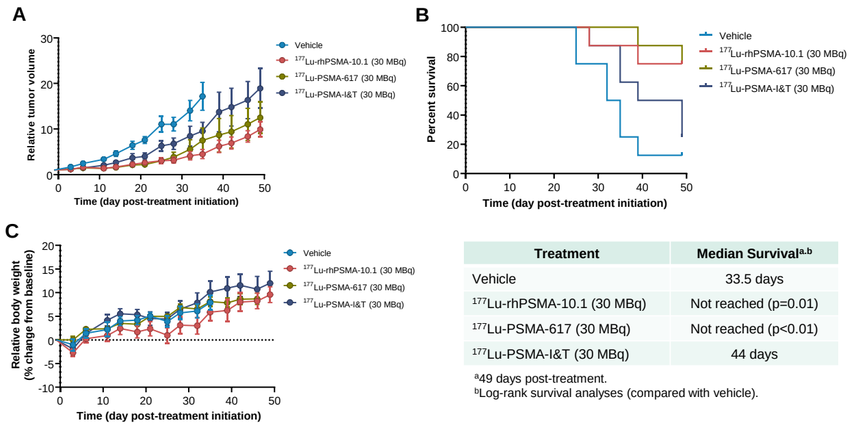
FIGURE 2. Relative tumor growth (A), survival (B) and relative body weight (C) after administration of ^{177}Lu-rhPSMA-10.1 in LNCaP xenografts



Treatment	Median Survival[a,b]
Vehicle	28 days
^{177}Lu-rhPSMA-10.1 (15 MBq)	Not reached ($p<0.01$)
^{177}Lu-rhPSMA-10.1 (30 MBq)	Not reached ($p<0.001$)
^{177}Lu-rhPSMA-10.1 (45 MBq)	Not reached ($p<0.01$)

[a]49 days post-treatment.
[b]Log-rank survival analyses (compared with vehicle).

FIGURE 3. Relative tumor growth (A), survival (B), and relative body weight (C) after treatment with ^{177}Lu-rhPSMA-10.1, ^{177}Lu-PSMA-617, or ^{177}Lu-PSMA-I&T in 22Rv1 xenografts



Treatment	Median Survival[a,b]
Vehicle	33.5 days
^{177}Lu-rhPSMA-10.1 (30 MBq)	Not reached ($p=0.01$)
^{177}Lu-PSMA-617 (30 MBq)	Not reached ($p<0.01$)
^{177}Lu-PSMA-I&T (30 MBq)	44 days

[a]49 days post-treatment.
[b]Log-rank survival analyses (compared with vehicle).

CONCLUSIONS

- **^{177}Lu-rhPSMA-10.1** was **well tolerated,** with **significant therapeutic efficacy** at clinically and sub-clinically equivalent dose levels in prostate cancer xenografts.
- The **promising therapeutic profile** of **^{177}Lu-rhPSMA-10.1**, compared with ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T further supports clinical development of **^{177}Lu-rhPSMA-10.1**, which is currently being evaluated in a Phase 1/2 clinical trial (**NCT05413850**).

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