Preclinical evaluation of a novel radioligand therapy for patients with prostate cancer: biodistribution and efficacy of ^{177}Lu-rhPSMA-10.1 in comparison with ^{177}Lu-PSMA-I&T

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Introduction

Challenge

- Radioligand therapy targeting prostate-specific membrane antigen (PSMA) has been shown to be an effective therapy in men with metastatic castration-resistant prostate cancer[1]
- However, optimizing tumor uptake and accelerating renal clearance for this class of compounds could improve the therapeutic index, achieve better clinical outcomes, and satisfy ALARA requirements to most effectively manage patient's radiation exposure

Objectives

- Identify a PSMA-targeting compound for radioligand therapy with improved biodistribution to:
  1. Maximize tumor uptake
  2. Minimize kidney uptake and retention

1. Sartor et al. NEJM. 2021;385:1091-1103.

Optimization of radiohybrid prostate-specific membrane antigen (rhPSMA) ligands for therapeutic use

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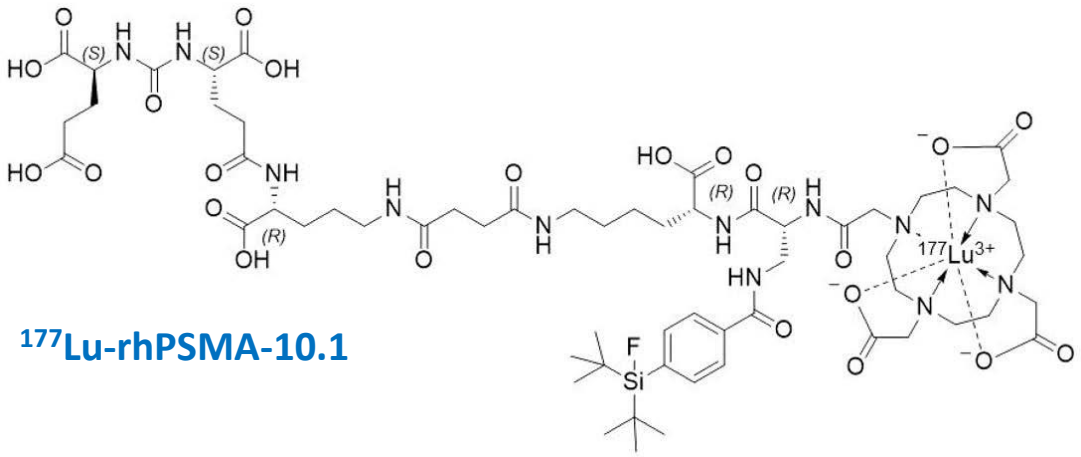
rhPSMA platform: two binding sites for radionuclides enabling theranostic potential

- Radiolabel with ^{18}F for diagnostic imaging (Phase 3 studies completed)
- Radiolabel with alpha- or beta-emitting radiometals for systemic radiation therapy
- Optimal properties differ for diagnostic imaging vs therapy
- Extensive Lead Optimization undertaken to select clinical candidate for therapeutic use



^{177}Lu-rhPSMA-10.1

Optimization of rhPSMA molecules to improve biodistribution:

- Increase affinity
- Optimize albumin binding
- Optimize overall charge

Novel rhPSMA radiopharmaceutical, ^{177}Lu-rhPSMA-10.1, selected for development as a potential therapeutic agent for prostate cancer

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Preclinical analyses: biodistribution and therapeutic efficacy of ^{177}Lu-rhPSMA-10.1 vs ^{177}Lu-PSMA-I&T

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1. Longitudinal biodistribution in non-tumor-bearing BALB/c mice

- 1 MBq of either radiopharmaceutical delivered via intravenous injection
- Tissues of interest were harvested for radioactivity measurement, 1, 12, 24, 48 and 168 h later
- N=4 mice per timepoint

2. Single-timepoint biodistribution to evaluate tumor:kidney uptake ratio in the 22Rv1 prostate cancer xenograft mouse model

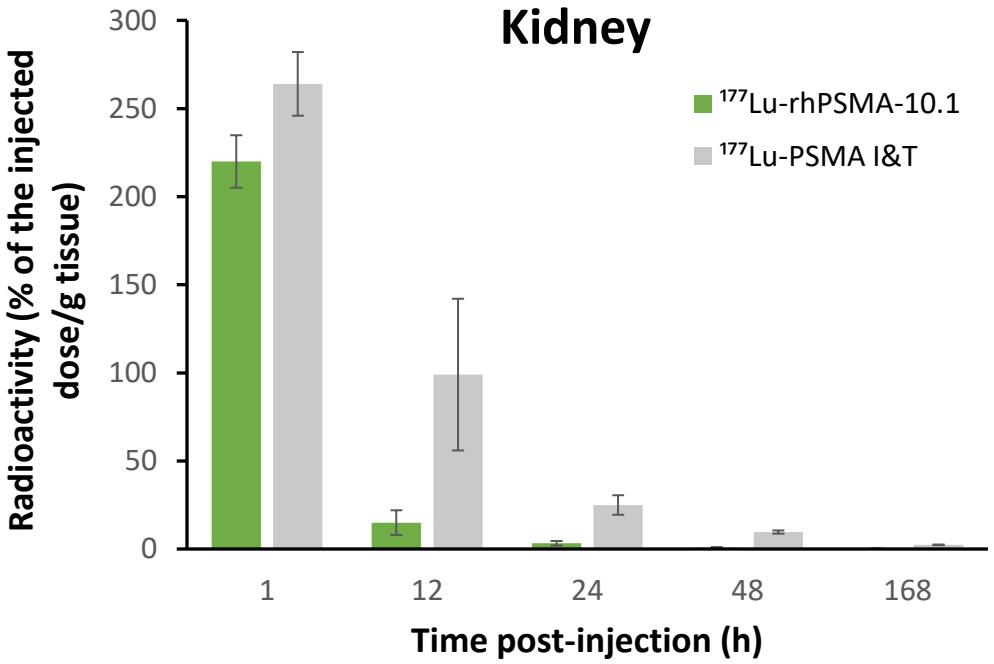
- 1 MBq of either radiopharmaceutical delivered via intravenous injection
- Tissues of interest were harvested 15 h later
- 22Rv1 tumor-bearing SCID mice, 22Rv1 express relatively low PSMA levels
- N=4 for ^{177}Lu-rhPSMA-10.1, n=3 for ^{177}Lu-PSMA-I&T

3. Efficacy in 22Rv1 tumor-bearing NMRI nu/nu mice

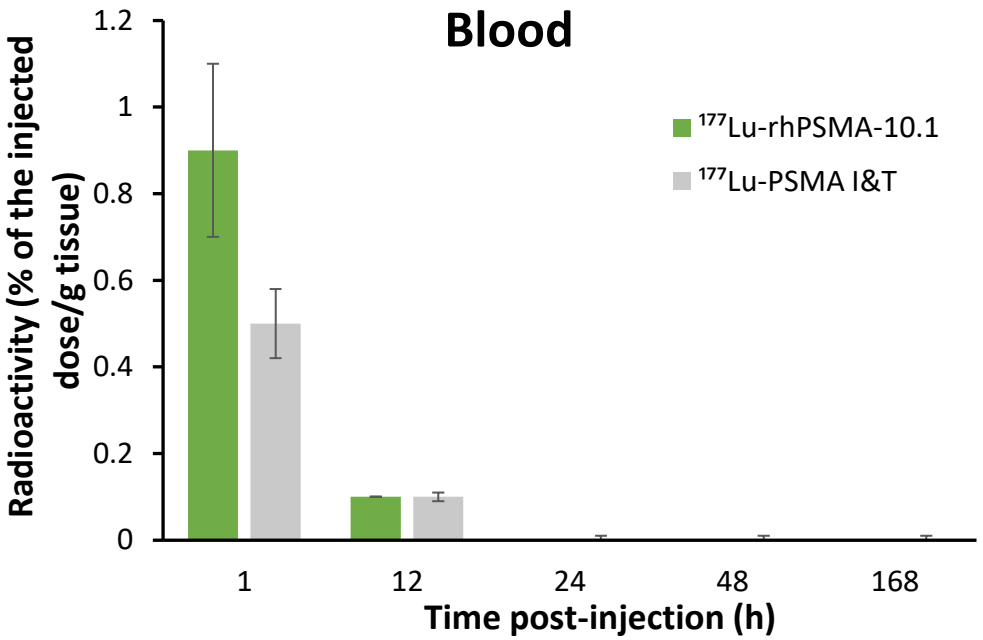
- Single intravenous injection of vehicle, either of the non-radiolabeled PSMA compounds, or either of the ^{177}Lu-radiolabeled PSMA compounds (30 MBq)
- Tumor volume and body weight were measured twice a week for 35 d
- Blood was collected on study days -1, 14 and 28 for hematological assessment
- N=8 per group

Results: longitudinal biodistribution in non-tumor-bearing BALB/c mice

- Significant kidney uptake was evident for both compounds, but was cleared over the study period
- Kidney uptake and retention was markedly lower for ^{177}Lu-rhPSMA-10.1 than ^{177}Lu-PSMA-I&T at all timepoints
- Levels of ^{177}Lu-rhPSMA-10.1 were 6.5-fold lower at 12 h



- Both ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-PSMA-I&T were rapidly cleared from the blood



No other organ (including the brain) showed any significant uptake of ^{177}Lu-rhPSMA-10.1

Chart presents mean ± standard deviation

Results: single-timepoint biodistribution in 22Rv1 tumor-bearing SCID mice

15 h post-injection

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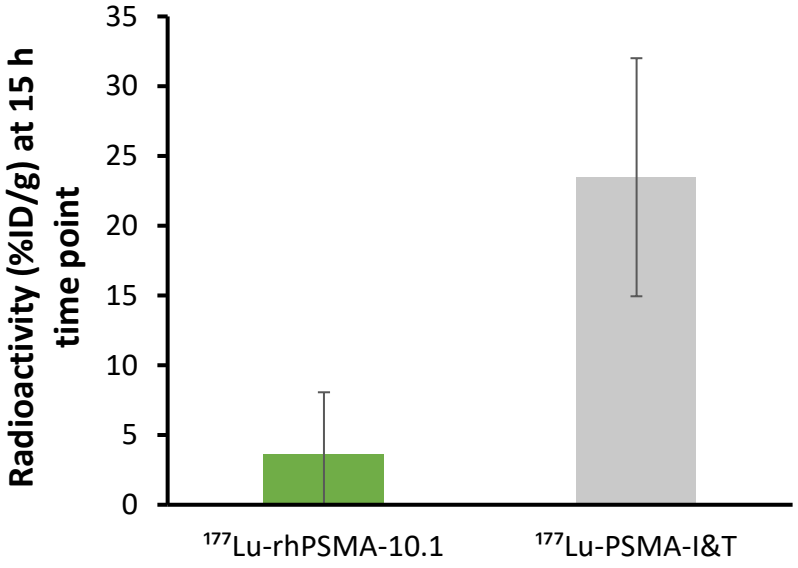
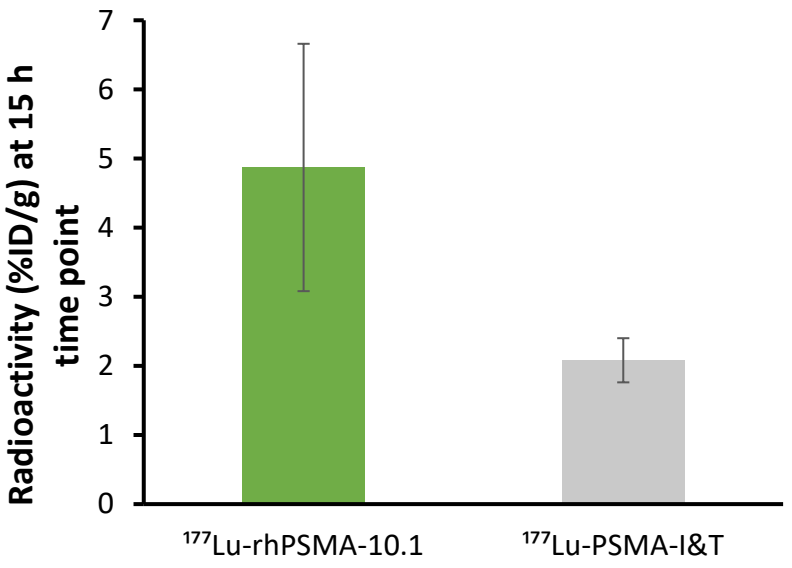
Kidney
Uptake was 6.4-fold lower for ^{177}Lu-rhPSMA-10.1 than for ^{177}Lu-PSMA-I&T

Tumor
Uptake was 2.3-fold higher for ^{177}Lu-rhPSMA-10.1 than for ^{177}Lu-PSMA-I&T

Tumor:kidney ratio
^{177}Lu-rhPSMA-10.1 showed a more favorable tumor:kidney ratio than ^{177}Lu-PSMA-I&T





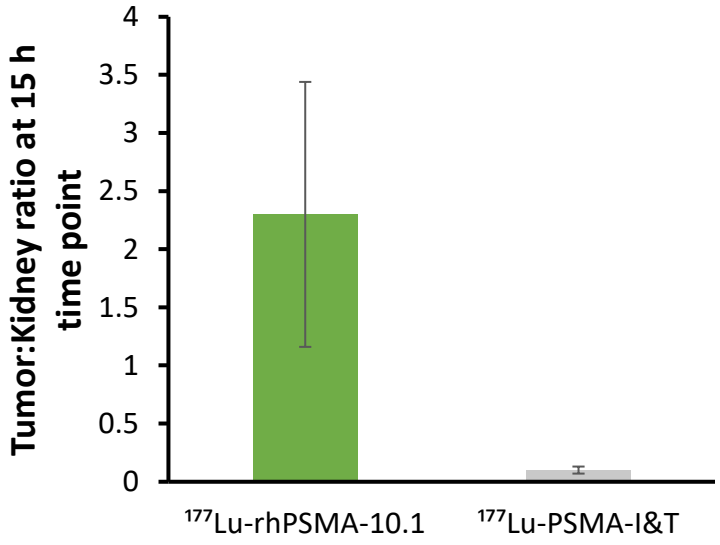


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Chart presents mean ± standard deviation

Results: mean tumor volume in 22Rv1 tumor-bearing NMRI nu/nu mice

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At 35 days post-treatment, the mean tumor volume was significantly reduced by ^{177}Lu-rhPSMA-10.1 compared with vehicle control

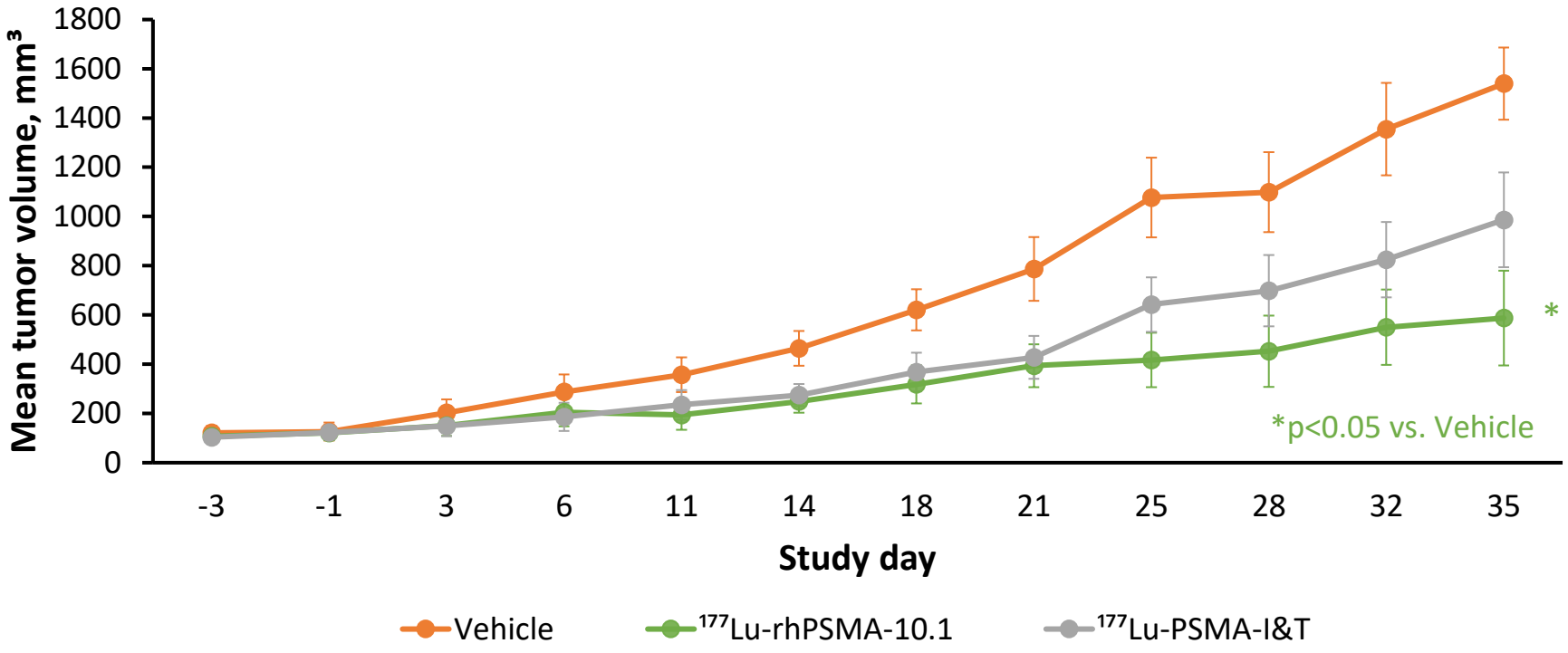
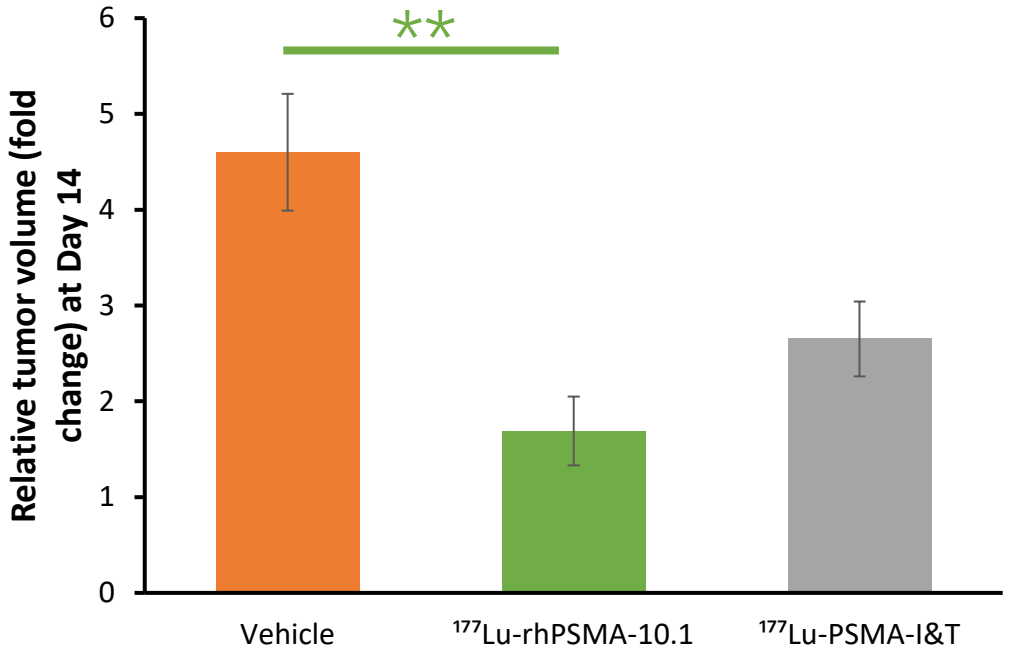
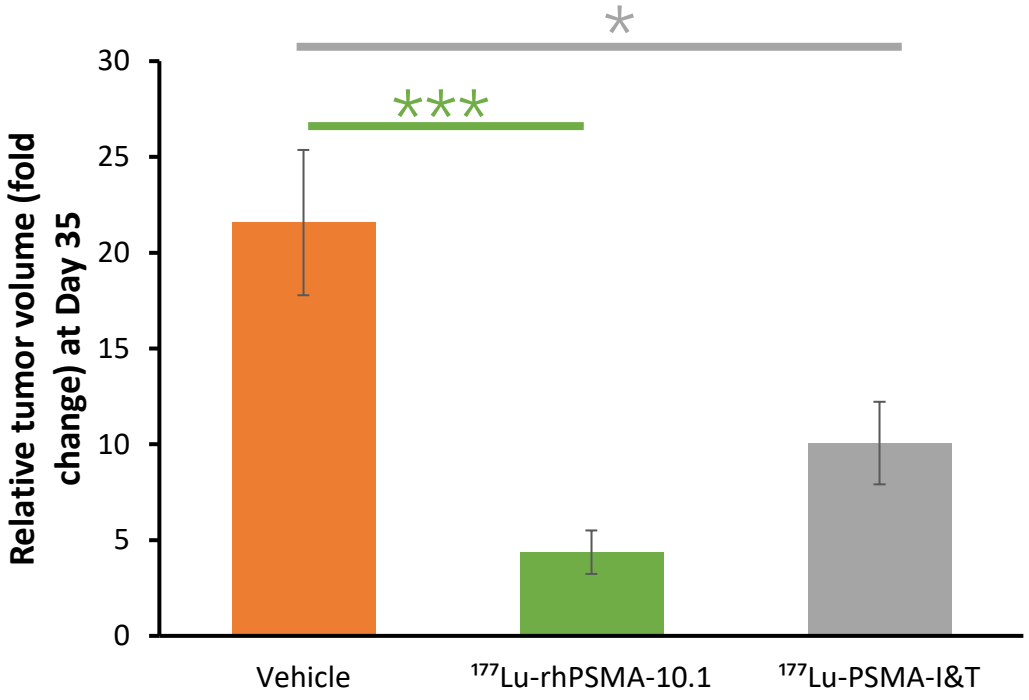


Chart presents mean ± standard error of the mean

Results: relative tumor volume in 22Rv1 tumor-bearing NMRI nu/nu mice

- ^{177}Lu-rhPSMA-10.1 significantly suppressed tumor growth vs vehicle at Day 14 and at Day 35
- ^{177}Lu-PSMA-I&T reduced tumor growth vs vehicle at Day 35, but to a lesser extent than ^{177}Lu-rhPSMA-10.1
- No significant effects were noted on any hematological parameters or body weight





*p<0.05, **p<0.01, ***p<0.001 (one-way ANOVA, Dunnett's multiple comparisons test [$]). Charts present mean ± standard error of the mean

[$] Seven groups included in the analysis, which included one additional ^{177}Lu-labeled test item and three non-radiolabeled precursor controls

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Conclusions

- ^{177}Lu-rhPSMA-10.1 performed favorably in biodistribution studies compared with ^{177}Lu-PSMA-I&T, with a markedly improved tumor:kidney ratio
- ^{177}Lu-rhPSMA-10.1 significantly suppressed tumor growth relative to control, and to a greater extent than ^{177}Lu-PSMA-I&T
- The favorable renal clearance of ^{177}Lu-rhPSMA-10.1 has since been confirmed in a minipig model that may be more representative of human physiology
- ^{177}Lu-rhPSMA-10.1 is currently undergoing study in a Phase 1/2 clinical trial (BET-PSMA-121)

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