

# AKY-2519, a Novel B7-H3-Targeted Radioconjugate, Demonstrates a Differentiated Biodistribution Profile with Low Normal Tissue Exposure and Robust Tumor Doses in Patients with mCRPC

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## INTRODUCTION

- Miniprotein binders enable novel radioconjugate therapy (RCT) that is optimized for high tumor penetration, internalization, and retention in cancer cells coupled with rapid plasma clearance to limit normal tissue exposure.
- AKY-2519 is a miniprotein-based RCT that targets B7-H3 (CD276) and can be chelated to imaging and therapeutic isotopes for patient selection and treatment (Fig. 1A, B).

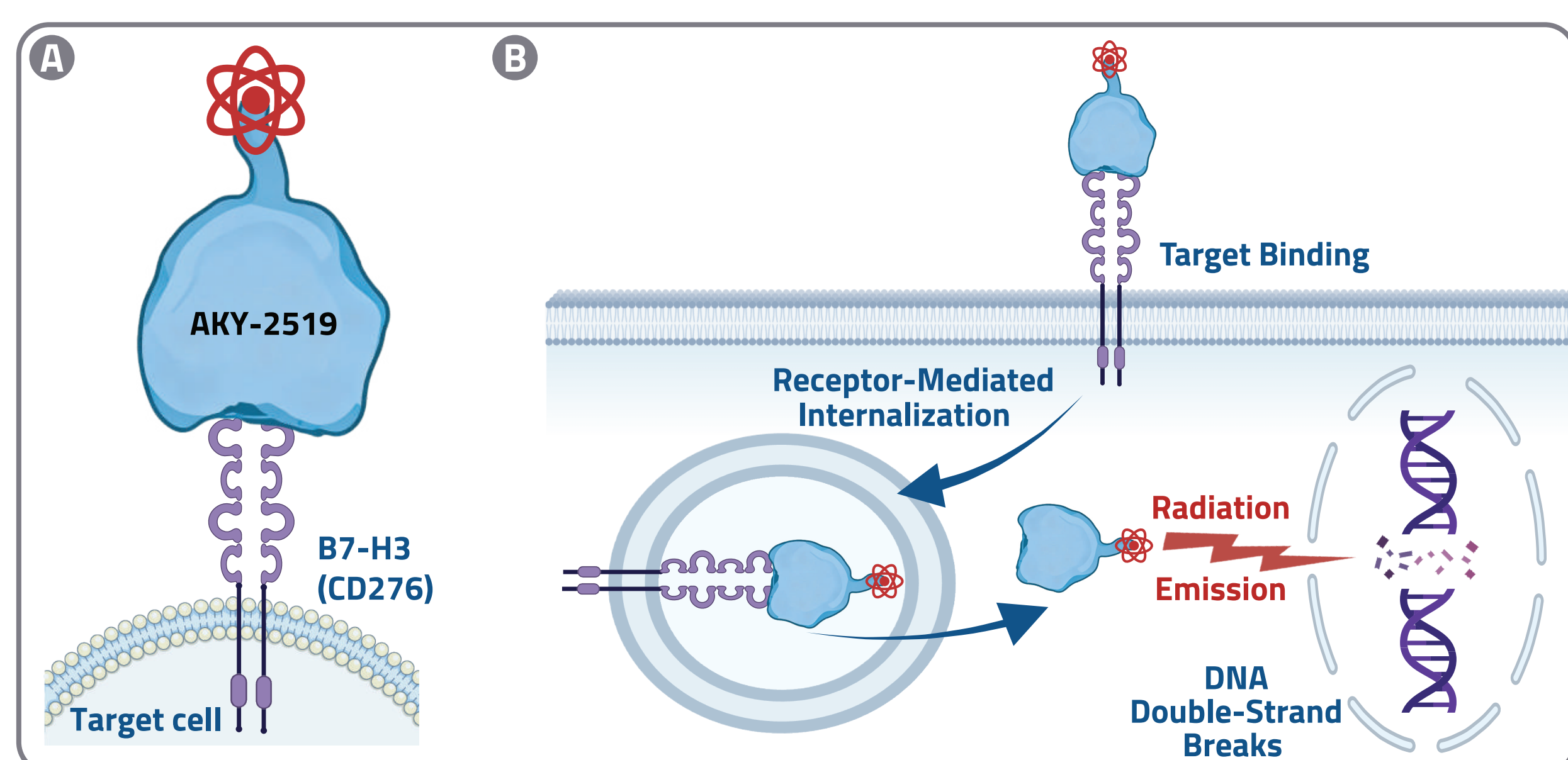


Figure 1. [<sup>225</sup>Ac]Ac-AKY-2519 RCT binds to B7-H3 on tumor cells (A) and results in cell death through radioactive decay (B).

- AKY-2519 is being investigated in a broad Phase 1b program as a theranostic pair utilizing Actinium-225 ([<sup>225</sup>Ac]Ac-AKY-2519) for therapy and Cu-64 for imaging ([<sup>64</sup>Cu]Cu-AKY-2519).
- B7-H3 is highly expressed in multiple solid tumor types, including metastatic castration resistant prostate cancer (mCRPC), and shows restricted expression in normal tissues.<sup>1-6</sup>
- Lack of B7-H3 expression in normal tissues such as the kidney and salivary glands suggests a wide therapeutic index for a B7-H3-targeting RCT.
- Here, we present the first human imaging and dosimetry data for a B7-H3 targeted radiopharmaceutical.

## AIMS

- To evaluate the biodistribution and dosimetry of [<sup>225</sup>Ac]Ac-AKY-2519 using [<sup>177</sup>Lu]Lu-AKY-2519 as a surrogate, including estimation of absorbed doses to tumors and normal tissues.
- To assess the biodistribution of [<sup>68</sup>Ga]Ga-AKY-2519 relative to that of prostate-specific membrane antigen (PSMA)-targeted imaging agent [<sup>68</sup>Ga]Ga-PSMA-11.

## METHODS

- Imaging and dosimetry was performed in 16 patients with mCRPC at NuMeRI in Pretoria, South Africa (Fig. 2).
- [<sup>68</sup>Ga]Ga-PSMA-11 PET/CT imaging was performed in all patients as part of standard clinical care.

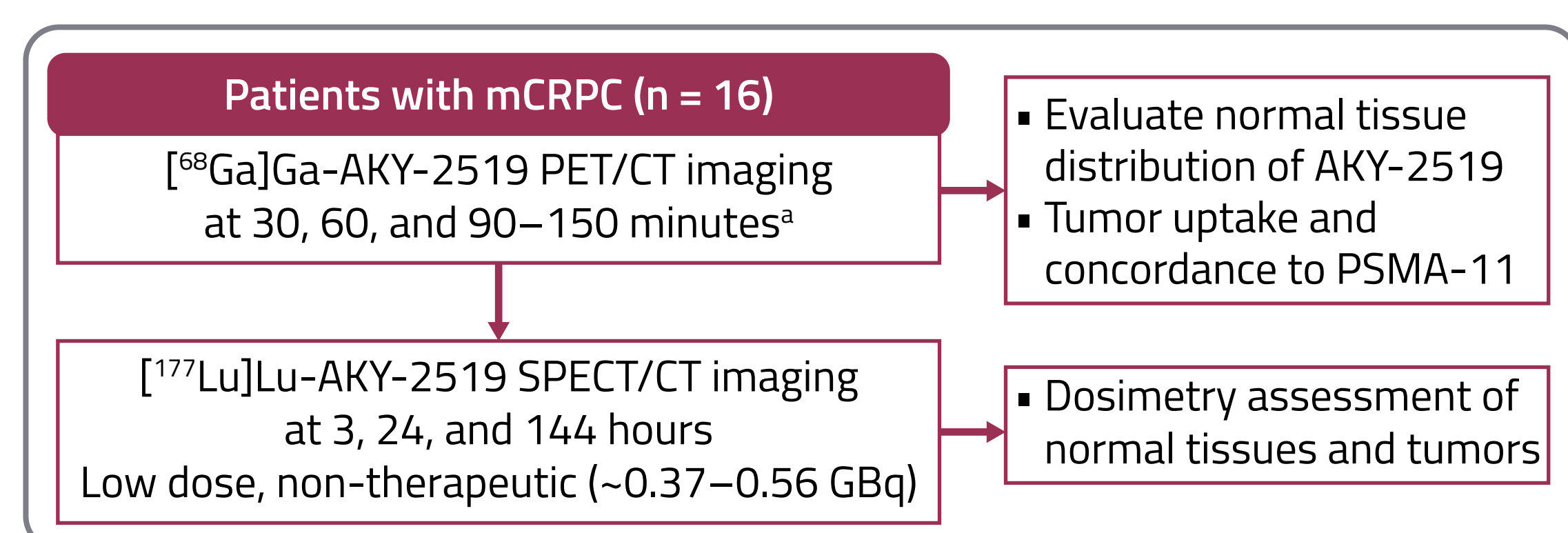


Figure 2. Flow of clinical imaging assessment at NuMeRI. <sup>a</sup>Imaging was performed at 30, 60, and 120 minutes for the first 14 patients and at 30, 60, 90, and 150 minutes for the last 2 patients.

- Multiple tumor and normal tissue regions of interest (ROI) were identified in each patient for evaluation of tumors with semi-quantitative metrics (SUV<sub>max</sub>) on [<sup>68</sup>Ga]Ga-AKY-2519 or [<sup>68</sup>Ga]Ga-PSMA-11 PET/CT images and for estimation of absorbed doses to tumors and normal tissues using [<sup>177</sup>Lu]Lu-AKY-2519 SPECT/CT.
- SPECT/CT images were reconstructed with MIM SPECTRA QUANT Software, comprehensive normal tissues identified with MIM Contour Protégé AI, and mean human [<sup>177</sup>Lu]Lu absorbed dose coefficients (Gy/GBq) were generated with MIM SurePlan™ MRT (GE Healthcare).
- Time-activity curves for [<sup>177</sup>Lu]Lu-AKY-2519 were subsequently decay corrected to account for differences in radioactive half-life between <sup>177</sup>Lu/<sup>225</sup>Ac, integrated to calculate the time-integrated activity coefficients, and input to OLINDA/EXM v2.4 to generate absorbed dose estimates for [<sup>225</sup>Ac]Ac-AKY-2519.
- Partial volume correction (PVC) in ROI analysis of tumors was performed using a dual contour approach, where the initial anatomic ROI was expanded by a 5 mm margin to generate a functional ROI recovering spill out activity.
- Total metabolic tumor burden was evaluated in select <sup>68</sup>Ga PET/CT images using a global liver-based SUV threshold and an automated lesion selection tool in MIM (LesionID). The SUV threshold was as described for soft tissues<sup>7</sup> and applied to both the [<sup>68</sup>Ga]Ga-AKY-2519 and [<sup>68</sup>Ga]Ga-PSMA-11 PET/CT images for comparison.

## RESULTS

### ADMINISTRATION OF AKY-2519 WAS GENERALLY WELL TOLERATED AND PREDICTS NORMAL TISSUE ABSORBED DOSES OF [<sup>225</sup>Ac]Ac-AKY-2519 BELOW ESTABLISHED CLINICAL BENCHMARKS

- No adverse events or infusion-related reactions were reported with either [<sup>68</sup>Ga]Ga-AKY-2519 or [<sup>177</sup>Lu]Lu-AKY-2519 administration.
- Absorbed doses to critical normal tissues (bone marrow, liver, kidneys, salivary glands) with [<sup>225</sup>Ac]Ac-AKY-2519 are estimated to be well below reference clinical benchmarks with a commonly utilized therapeutic administration schedule (8 MBq x 4)<sup>8</sup> (Table 1).
- Estimates of predicted absorbed dose to the salivary glands with [<sup>225</sup>Ac]Ac-AKY-2519 compare favorably to those reported for approved PSMA-targeting radiopharmaceutical.<sup>9</sup>
- Absorbed doses predicted for other normal tissues were low and not clinically meaningful (data not presented).

Table 1. Predicted [<sup>225</sup>Ac]Ac-AKY-2519 absorbed doses in critical normal tissues

Normal Tissue (n=12) <sup>a</sup>	Mean Absorbed Dose Coefficient ( <sup>225</sup> Ac) Gy <sub>RBE-5</sub> /MBq (SD)	Predicted Absorbed Dose at 8 MBq x 4 Gy <sub>RBE-5</sub>
Bone marrow	0.04 (0.02)	1.3
Liver	0.31 (0.10)	9.9
Kidneys	0.50 (0.17)	16
Salivary glands	0.13 (0.04)	4.2

<sup>a</sup>[<sup>177</sup>Lu]Lu-AKY-2519 was used as a surrogate for estimation of absorbed doses with [<sup>225</sup>Ac]Ac-AKY-2519. Of the 16 patients with [<sup>177</sup>Lu]Lu-AKY-2519 dosimetry data available, 12 had sufficient data for conversion to [<sup>225</sup>Ac]Ac-AKY-2519; RBE, relative biological effectiveness; SD, standard deviation.

### AKY-2519 DEMONSTRATES ROBUST TUMOR UPTAKE AND RETENTION WITH PREDICTED ABSORBED DOSES OF [<sup>225</sup>Ac]Ac-AKY-2519 SUGGESTING A WIDE THERAPEUTIC INDEX

- Uptake and prolonged retention in tumors out to at least 6 days has been demonstrated (Fig. 3).
- Predicted absorbed doses to selected tumors, including the involved prostate and seminal vesicles, as well as nodal and bony metastases, are within expected therapeutic ranges for approved radiopharmaceuticals (Table 2).<sup>10</sup>

Table 2. Estimated tumor absorbed doses of [<sup>225</sup>Ac]Ac-AKY-2519 in mCRPC lesions

Lesion Location	Evaluable Patients	Mean Absorbed Dose Coefficient <sup>a</sup> ( <sup>225</sup> Ac) Gy <sub>RBE-5</sub> /MBq (SD)	Mean Absorbed Dose Coefficient with PVC ( <sup>225</sup> Ac) Gy <sub>RBE-5</sub> /MBq (SD)	Predicted Absorbed Dose <sup>b</sup> at 8 MBq x 4 Gy <sub>RBE-5</sub> (SD)	Predicted Absorbed Dose <sup>b</sup> at 8 MBq x 4 with PVC Gy <sub>RBE-5</sub> (SD)
Involved prostate ± seminal vesicles	8	2.6 (1.2)	N/A <sup>c</sup>	83 (39)	N/A <sup>c</sup>
Nodal metastases	5	4.4 (2.8)	8.4 (4.2)	141 (88)	268 (134)
Bony metastases	6	1.5 (0.8)	3.8 (1.8)	48 (25)	121 (57)

<sup>a</sup>Where multiple ROIs of the same category were available in a single patient (nodal or bony metastasis), the highest value was utilized. <sup>b</sup>Projected absorbed dose estimates are calculated based on the corresponding raw dose coefficient for the region of interest. <sup>c</sup>Partial volume correction (PVC) was not applied for ROI analysis of involved prostate due to spillover activity from adjacent bladder. SD, standard deviation.

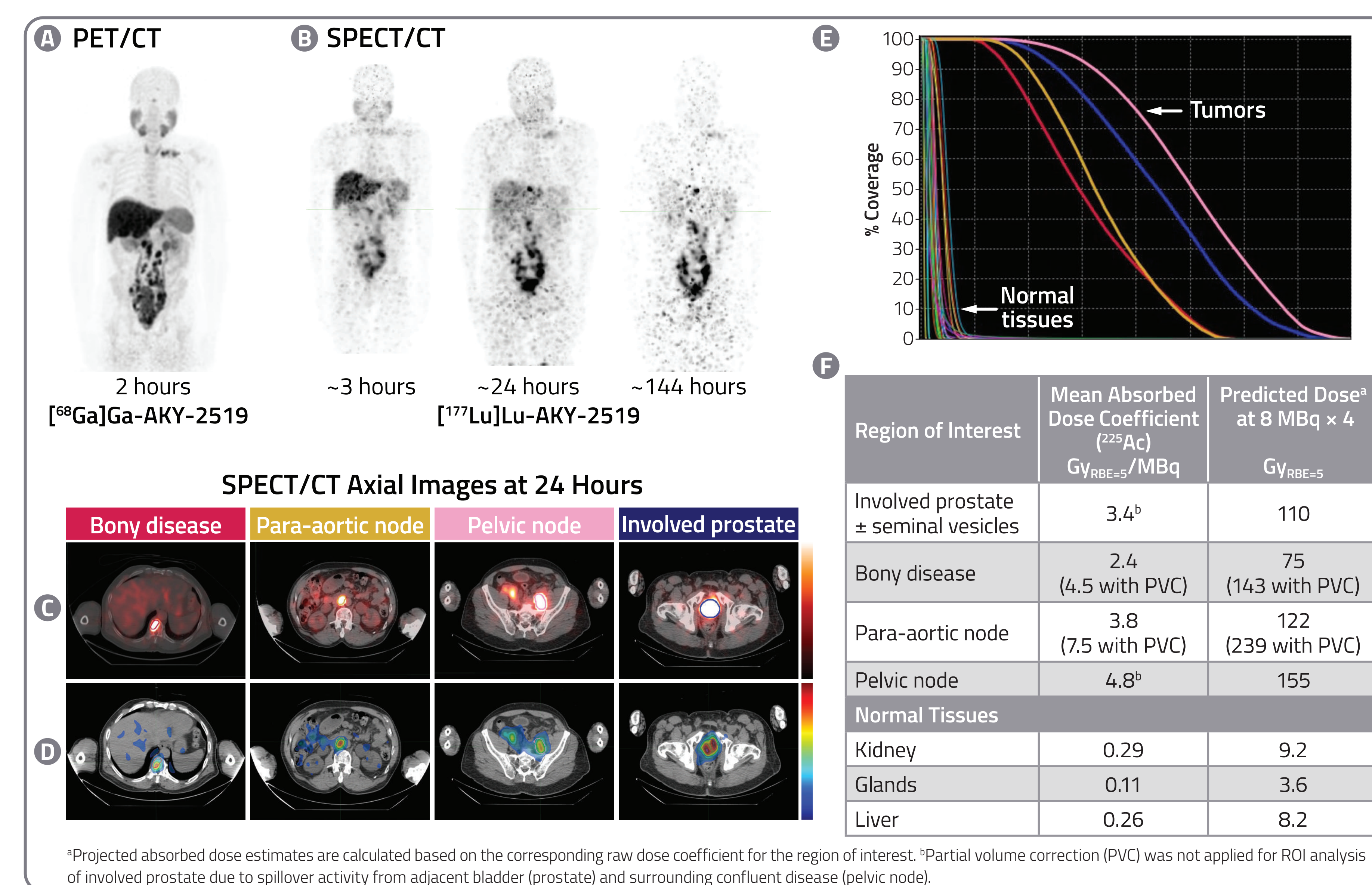


Figure 3. Patient with mCRPC, Gleason (3+4)=7, initial PSA of 1500 ng/mL, on ADT with rising PSA. PET/CT image 2 hours after [<sup>68</sup>Ga]Ga-AKY-2519 injection revealing robust tumor uptake (A) and SPECT-CT images 3, 24, and 144 hours after injection of 0.76 GBq (20.5 mCi) [<sup>177</sup>Lu]Lu-AKY-2519 showing retention of activity in metastatic lesions and no significant accumulation in normal tissues (B). Representative tumors selected for dosimetry are illustrated on the 24 hr axial SPECT images (C) with associated dose clouds (D). The wide therapeutic index predicted by the absorbed dose to tumors relative to normal tissues can be seen in the accompanying dose-volume histogram (E) as well as the [<sup>225</sup>Ac]Ac-AKY-2519 conversions described in table (F). ADT, androgen deprivation therapy; PSA, prostate-specific antigen.

### [<sup>68</sup>Ga]Ga-AKY-2519 CONSISTENTLY IDENTIFIES LESIONS ALSO IDENTIFIED BY [<sup>68</sup>Ga]Ga-PSMA-11

- Distribution of tumor uptake appears comparable between B7-H3 targeting [<sup>68</sup>Ga]Ga-AKY-2519 and [<sup>68</sup>Ga]Ga-PSMA-11 (Fig. 4) at the standard acquisition time of ~60 minutes.
- Tumor uptake with [<sup>68</sup>Ga]Ga-AKY-2519 appears to increase over time.
- Additional analyses will be conducted to further characterize relative uptake.

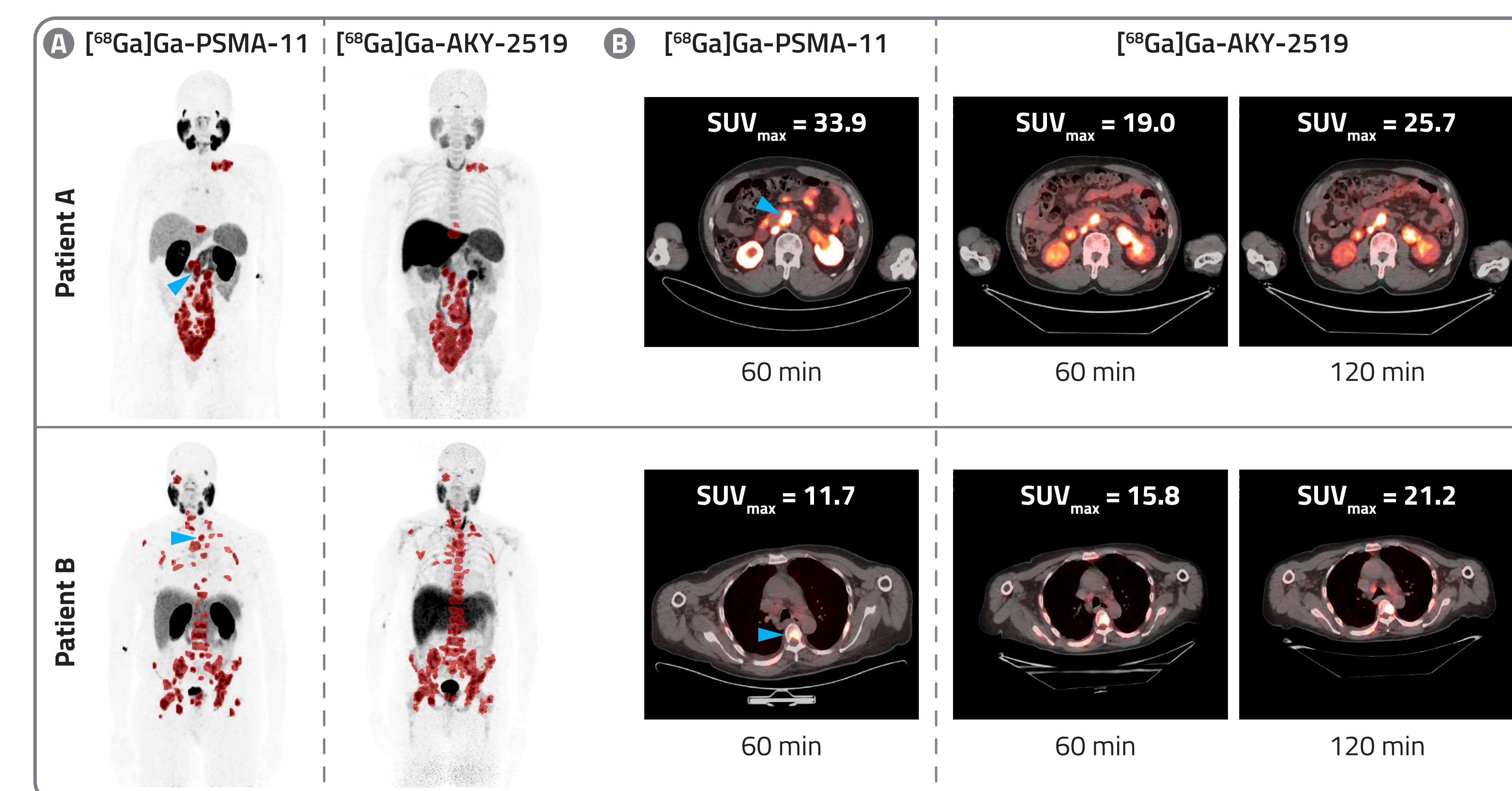


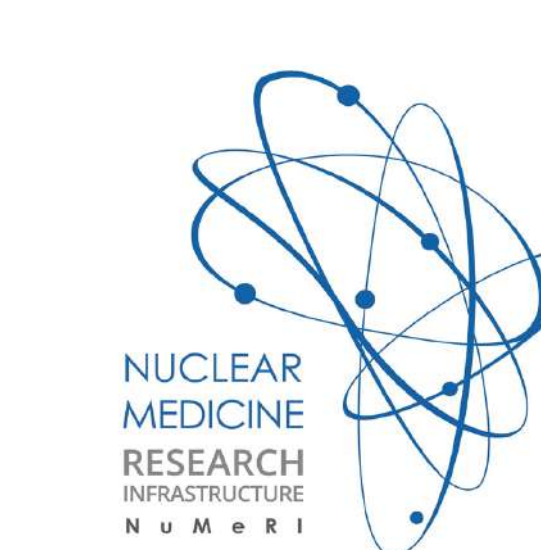
Figure 4. Comparative [<sup>68</sup>Ga]Ga-AKY-2519 and [<sup>68</sup>Ga]Ga-PSMA-11 PET/CT imaging in patients with mCRPC. (A) Maximum intensity projection (MIP) PET images for two representative patients (Patient A, Patient B) at 60 min post administration) with total metabolic tumor burden overlaid in red, following RECIP 1.0 guidelines. Blue arrows highlight disease sites for which (B) transaxial slices are shown to demonstrate tumor uptake and retention. [<sup>68</sup>Ga]Ga-PSMA-11 completed 5-6 weeks prior to [<sup>68</sup>Ga]Ga-AKY-2519 in (A) and 1 day prior in (B). All PET images are displayed on a scale of 0 to 12 SUV.

## CONCLUSIONS

These are the first clinical biodistribution and dosimetry data suggesting that an <sup>225</sup>Ac-labeled miniprotein binder targeting B7-H3 is expected to deliver therapeutic doses to tumors at well-tolerated normal tissue absorbed doses.

- Normal tissue and tumor absorbed doses observed with AKY-2519 suggest a wide window exists for therapeutic delivery of Actinium-225.
- The low predicted absorbed dose to salivary glands may differentiate an AKY-2519 RCT from other PSMA-targeted agents.
- PET-CT imaging analyses show good agreement in identification of tumors between PSMA-11 and AKY-2519.
- These results support the clinical development of AKY-2519 as an <sup>225</sup>Ac-delivering RCT for patients with B7-H3 expressing mCRPC.
- A Phase 1b clinical trial of [<sup>225</sup>Ac]Ac-AKY-2519 in mCRPC has been initiated (NCT07581184) and a second Phase 1b trial evaluating [<sup>225</sup>Ac]Ac-AKY-2519 in lung cancers, colorectal cancer, and other B7-H3 expressing tumor types is expected to start in 2H-2026
- Clinical imaging data on the biodistribution and tumor uptake of AKY-2519 in other solid tumor types is reported in Poster 3098.

References: 1) Seaman S, et al. *Cancer Cell*. 2017;31(4):501-515.e508. 2) Zhou WT, jin WL. *Front Immunol*. 2021;12:701006. 3) Kontos F, et al. *Clin Cancer Res*. 2021;27(5):1227-1235. 4) Guo C, et al. *Eur Urol*. 2023;83(3):224-238. 5) Kang N, et al. *Cancer Gene Ther*. 2023;30(10):1382-1389. 6) Amori G, et al. *Prostate Cancer Prostatic Dis*. 2021;24(3):767-774. 7) Gafita A, et al. *J Nucl Med*. 2019;60(9):1277-1283. 8) Wahl RL, et al. *J Nucl Med*. 2021;62(Suppl 3):235-35s. 9) Pluvicto (lutetium Lu 177 vipivotide tetraxetan) injection [package insert]. Novartis Pharmaceuticals Corporation, 03/2025. 10) Ellis Z, et al. *J Nucl Med*. 2024;65(8):1264-1271.



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