

First-in-Human PET/CT Imaging With [⁶⁸Ga]Ga-AKY-2519, a B7-H3-Targeted Miniprotein Radioconjugate, to Demonstrate Tumor Uptake and Normal Tissue Exposure Across Various Advanced Solid Tumors

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INTRODUCTION

- Miniproteins are binders used to generate novel radioconjugate therapy (RCT) assets optimized for high affinity, selectivity, deep tumor penetration, and internalization into tumor cells
- Together with rapid plasma clearance, these characteristics facilitate prolonged tumor retention with limited exposure to normal tissues (Table 1).

Table 1. Properties of AKY-2519

Affinity	Recombinant human B7-H3 (K _D)		On-cell binding (K _D)	
	0.45 ± 0.17 nM ^a		0.87 ± 0.37 nM ^a	
Selectivity	Protein array		On-cell	
	No binding to 6500+ surface proteins ^b		No binding to B7-H3 CRISPR KO cells	
Pharmacokinetics ^c	T _{1/2} (min)	AUC _{inf} (min*ng/mL)	CL (mL/min/kg)	V _{ss} (mL/kg)
	54.7 (2.4)	16695 (638)	5.9 (0.25)	366 (44.3)
In vitro stability	KBBM assay (Human)		Human plasma	
	>12 hours		>12 hours	
Binder toxicology	Non-GLP single dose rat		GLP single dose minipig	
	NOAEL defined as 500x allometrically scaled human dose ^d		NOAEL defined as 1000x allometrically scaled human dose ^d	

^aBiotin-AKY-2519 was used to generate affinity measurements. ^bSelectivity of biotin-AKY-2519 for B7-H3 was verified across 6500+ human cell surface and secreted proteins using Retrogenx Cell Microarray Technology with >350-fold selectivity over demonstrated K_D. ^cPharmacokinetic analysis of La-AKY-2519 in Sprague-Dawley rats after single-dose intravenous administration (0.1 mg/kg dose). Noncompartmental analysis reported values ± standard error. ^dAllometrically scaled predicted gender averaged absorbed doses using biodistribution data from [¹¹¹In]-AKY-2519 SPECT/CT studies in mice. AUC_{inf}, area under the curve; CL, clearance; V_{ss}, steady-state volume distribution; KBBM, kidney brush border membranes; GLP, Good Laboratory Practices; NOAEL, no-observed-adverse-effect-level.

- AKY-2519 is a miniprotein-based RCT that targets B7-H3 (CD276) and can be chelated to imaging isotopes for evaluation of biodistribution and patient selection, and to therapeutic isotopes for RCT (Fig. 1A, B).

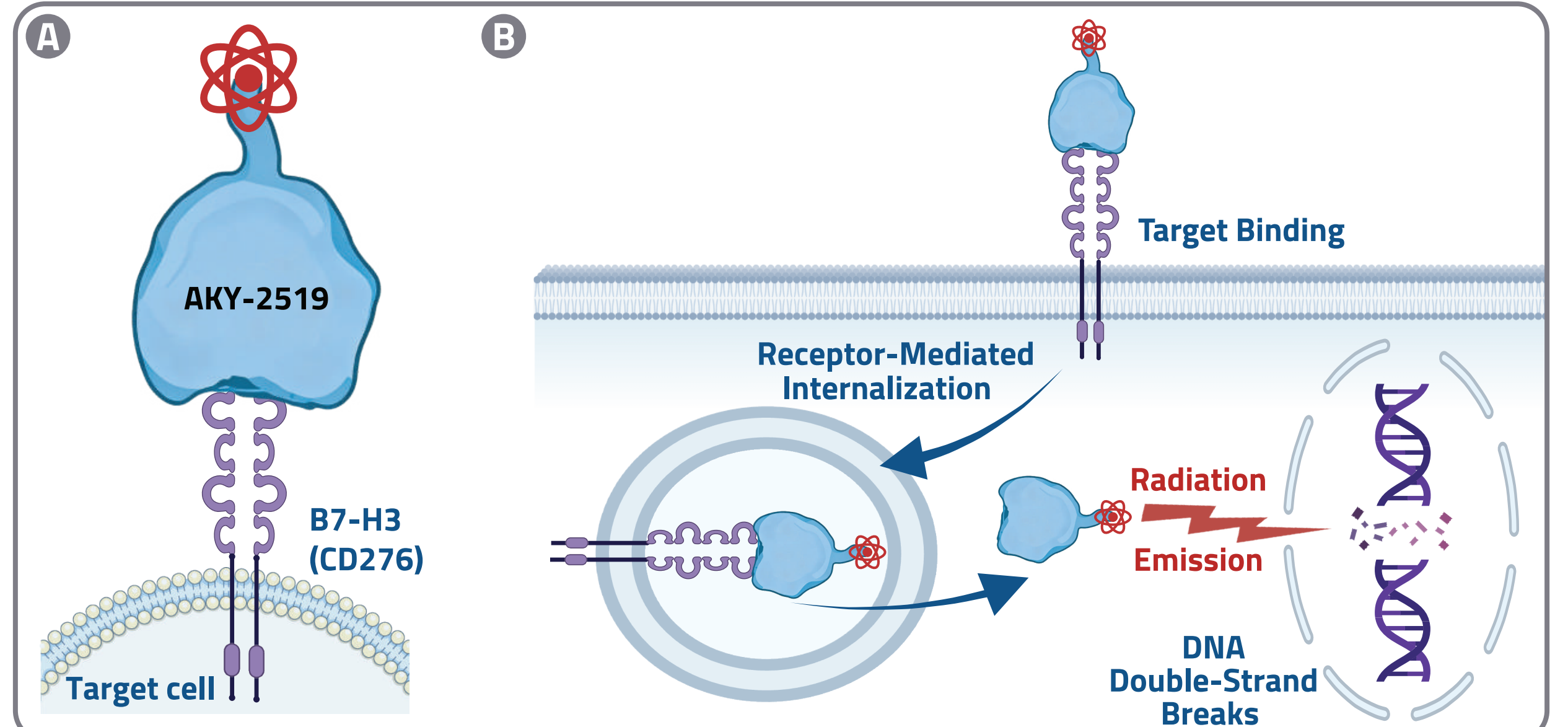


Figure 1. [²²⁵Ac]Ac-AKY-2519 miniprotein-based targeted radioconjugate (A) and the therapeutic mechanism of action of [²²⁵Ac]Ac-AKY-2519 (B).

- AKY-2519 is being investigated in a broad Phase 1b program as a theranostic pair utilizing Actinium-225 (²²⁵Ac-AKY-2519) for therapy and Copper-64 for imaging (⁶⁴Cu-AKY-2519).
- B7-H3 is overexpressed in many solid tumors and has limited expression in normal tissues.¹⁻⁶
- Several anti-B7-H3 antibody-drug conjugates have shown objective responses and durable disease control in early-phase studies in patients with solid tumors.^{3,4,7}
- This AKY-2519 clinical imaging assessment provides a first look at the biodistribution of a miniprotein radioconjugate targeting B7-H3 across a variety of solid tumors.

AIM

- To evaluate the biodistribution and tumor uptake of [⁶⁸Ga]Ga-AKY-2519 in patients with a variety of solid tumors.

METHODS

- Prospective, observational imaging study in patients with prostate, colorectal, lung cancer, and other solid tumors at University Hospital Essen, Essen, Germany.
- Multiple regions of interest (ROI) were selected within each patient for evaluation of activity.
- Semi-quantitative metrics (SUV_{max}, SUV_{mean}, SUV_{peak}) were utilized to assess tumor uptake and normal tissue distribution at 15, 60, and 120 minutes following intravenous administration of [⁶⁸Ga]Ga-AKY-2519 (administered activity 142 [92] MBq (median [IQR])).
- Imaging findings were correlated with prostate-specific membrane antigen (PSMA) targeted imaging agent (⁶⁸Ga]Ga-PSMA or [¹⁸F]-PSMA) and [¹⁸F]-fluoro-2-deoxy-d-glucose (¹⁸F-FDG) reference PET/CTs where available.

RESULTS

ADMINISTRATION OF [⁶⁸Ga]Ga-AKY-2519 WAS GENERALLY WELL TOLERATED ACROSS A LARGE COHORT OF PATIENTS WITH DIVERSE SOLID TUMORS

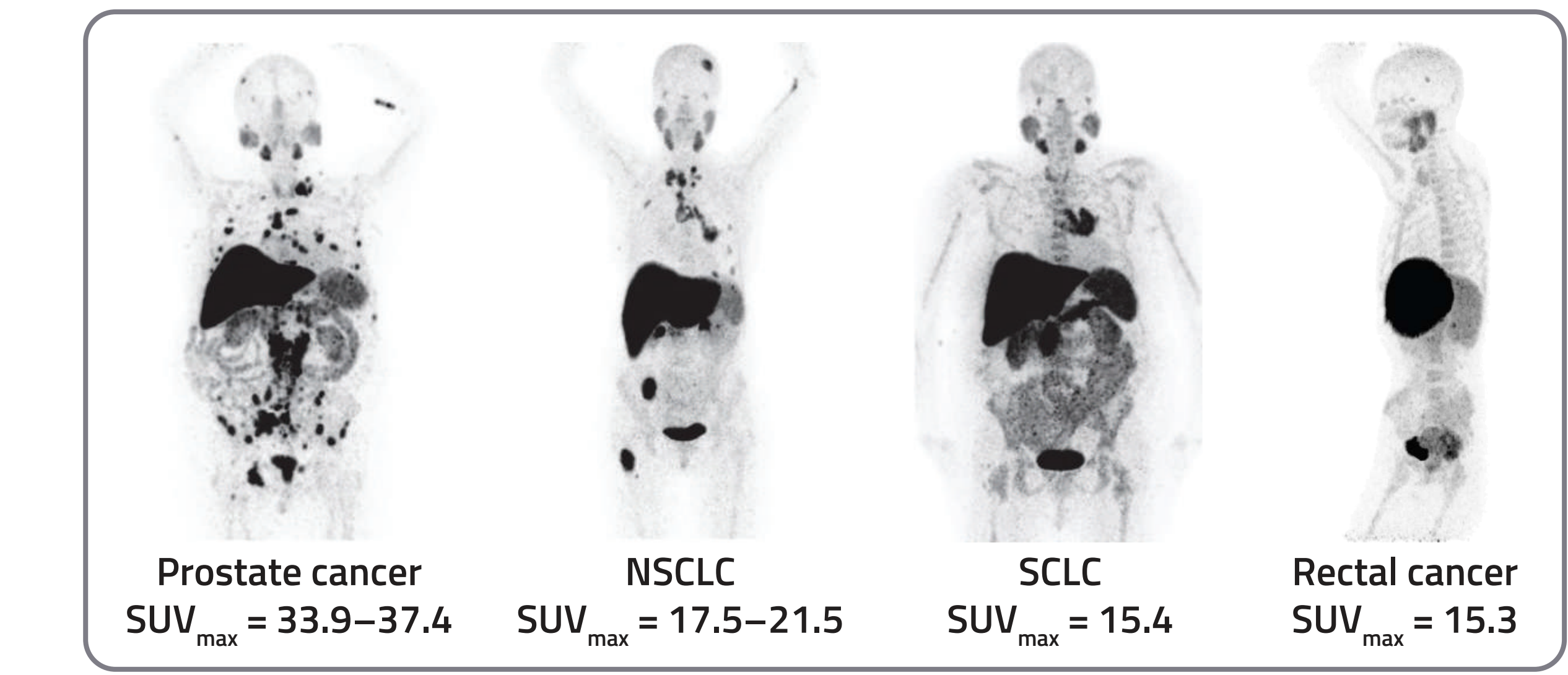
- 18 patients with advanced or metastatic disease were imaged across prostate, lung, colorectal, and other tumor types (Table 2).
- No adverse events or infusion-related reactions were reported during the imaging assessment.

Table 2. Patient Characteristics

Patient Characteristics	Total (n=18)	Patient Characteristics	Total (n=18)	
Age, median (range), years	66 (36–77)	Surgery	8	
Sex, n	Male	12	Chemotherapy	8
	Female	6	Radiotherapy	7
Tumor Types, n (%)	mHSPC/mCRPC	7 (38.9)	Radiorigand therapy	2
	SCLC	3 (16.7)	Hormone therapy	6
	NSCLC	1 (5.6)	Immunotherapy	3
	CRC	4 (22.2)	UICC I-III	11
	Other ^a	3 (16.7)	UICC IV	7
		Prior Treatment, n		
		Initial Stage, n		

^aIncluding intrahepatic cholangiocarcinoma, urothelial carcinoma, and undifferentiated adenocarcinoma. CRC, colorectal cancer; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; UICC, Union for International Cancer Control.

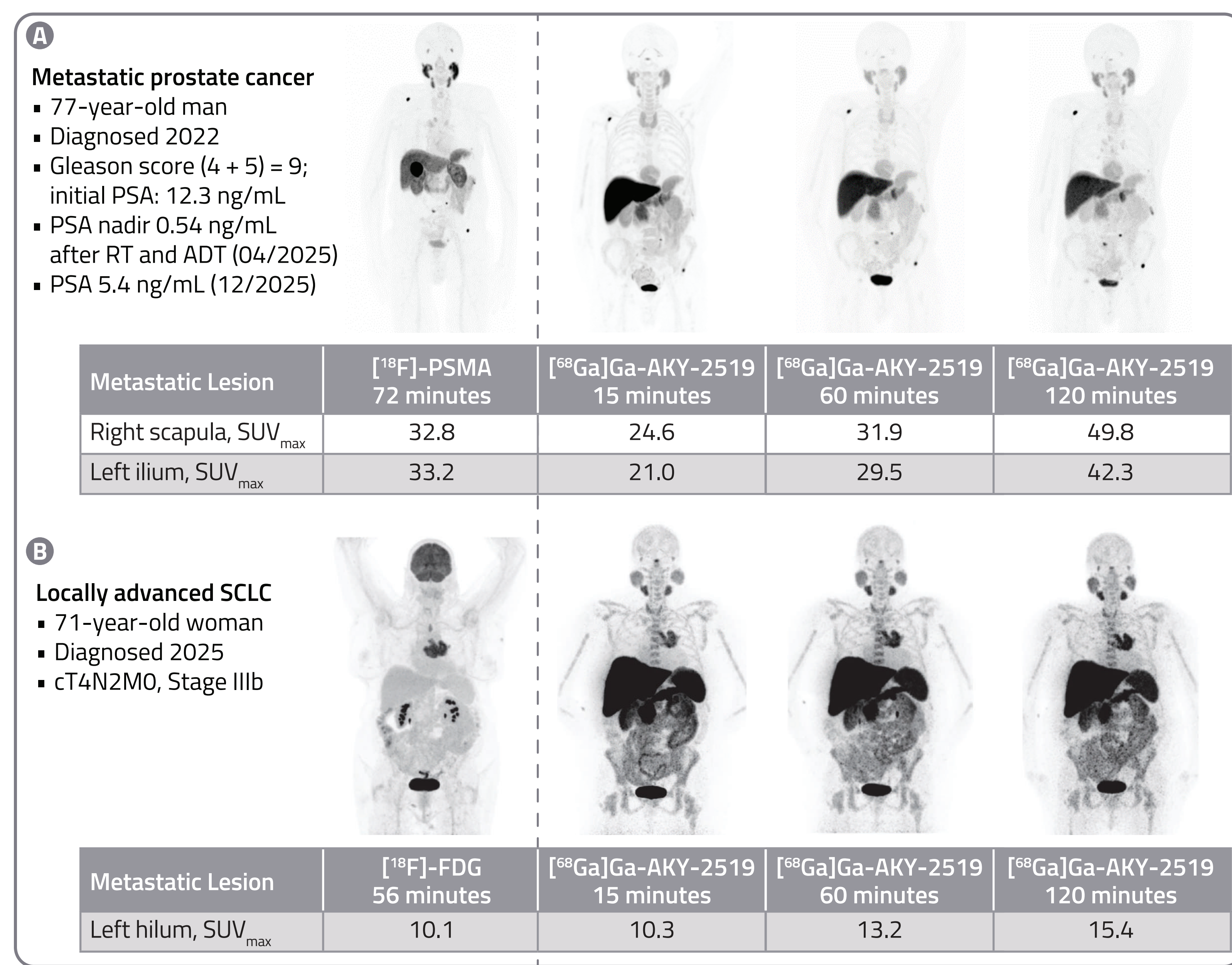
[⁶⁸Ga]Ga-AKY-2519 DEMONSTRATES ROBUST TUMOR UPTAKE IN A VARIETY OF SOLID TUMORS



- Uptake of [⁶⁸Ga]Ga-AKY-2519 was observed across multiple tumor types at various time points.
- SUV_{max} values for selected tumors compares favorably to those of approved radiopharmaceuticals (Fig. 2).⁸

Figure 2. Representative patients across solid tumor types with robust tumor uptake at 120 minutes following [⁶⁸Ga]Ga-AKY-2519 administration.

TUMOR DISTRIBUTION AND INTENSITY OF [⁶⁸Ga]Ga-AKY-2519 UPTAKE COMPARES FAVORABLY WITH STANDARD OF CARE IMAGING



- Tumor uptake on [⁶⁸Ga]Ga-AKY-2519 imaging appears to align well with both PSMA and FDG reference images (Fig. 3).
- [⁶⁸Ga]Ga-AKY-2519 uptake, as evidenced by SUV_{max} values, is comparable to standard of care imaging at the one hour timepoint.
- Comparison of 15, 60, and 120 minute [⁶⁸Ga]Ga-AKY-2519 PET/CT scans demonstrate an increase in tumor uptake over time.

Figure 3. Representative images comparing [⁶⁸Ga]Ga-AKY-2519 PET/CT images with standard of care in prostate cancer (A) and locally advanced SCLC (B). ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RT, radiotherapy.

[⁶⁸Ga]Ga-AKY-2519 UPTAKE WAS CONSISTENTLY OBSERVED AT HIGH LEVELS ACROSS METASTATIC DISEASE SITES IN PATIENTS WITH PROSTATE CANCER

- Summary data was compiled for the largest cohort of patients (mHSPC/mCRPC) across multiple ROIs.
- Consistently high SUV values were observed across metastatic sites, with the most intense uptake observed in bone and visceral metastasis (Table 3).

Table 3. Uptake of [⁶⁸Ga]Ga-AKY-2519 (120 min post infusion) in multiple metastatic disease sites from patients with prostate cancer (n=7)

	Bone Metastases	Lymph Node Metastases	Visceral Metastases
Median SUV _{max}	40.4	13.8	31.0
Median SUV _{peak}	25.0	6.5	22.2
Median SUV _{mean}	16.1	5.1	18.7

SUV, standardized uptake value.

[⁶⁸Ga]Ga-AKY-2519 UPTAKE IN NORMAL TISSUES SUGGESTS A WIDE THERAPEUTIC INDEX

- PET/CT imaging 120 min after [⁶⁸Ga]Ga-AKY-2519 injection showed low uptake in critical normal tissues (Table 4).
- Initial activity in the liver was noted to clear rapidly in another clinical imaging assessment incorporating later timepoints (see Poster 3097).

Table 4. Uptake of [⁶⁸Ga]Ga-AKY-2519 (120 min post infusion) in normal tissues of patients with solid tumors (n=18)

	Adrenal Glands	Bone Marrow	Kidneys	Liver	Salivary Glands	Spleen
Median (IQR) SUV _{max}	17.5 (15.9–19.8)	4.1 (3.3–5.1)	6.7 (6.3–8.7)	22.9 (20.9–30.8)	7.3 (6.4–11.4)	9.2 (7.6–10.4)

CONCLUSIONS

- These are the first clinical imaging data showing that the AKY-2519 miniprotein-based RCT targeting B7-H3 demonstrates robust tumor uptake across a variety of solid tumor types.
- Low uptake in critical normal tissues suggests that a wide window exists for therapeutic delivery.
- These imaging results and additional AKY-2519 dosimetry results (Poster 3097) support the clinical development of AKY-2519 as an ²²⁵Ac-delivering RCT for patients with B7-H3 expressing solid tumors.
- A Phase 1b clinical trial of [²²⁵Ac]Ac-AKY-2519 in mCRPC has been initiated (NCT07581184) and a second Phase 1b trial evaluating [²²⁵Ac]Ac-AKY-2519 in lung cancers, colorectal cancer, and other B7-H3 expressing tumor types is expected to start in 2H-2026.

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