

MTTI's Radiopharmaceuticals

A NEW GENERATION OF TARGETED RADIOTHERAPEUTICS (TRT)

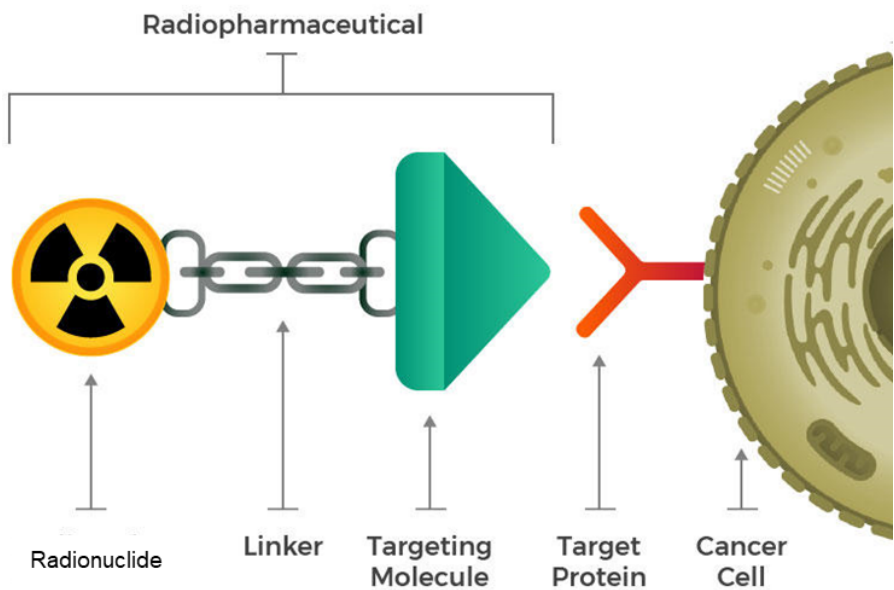
Chris Pak

cpak@mtarget.com



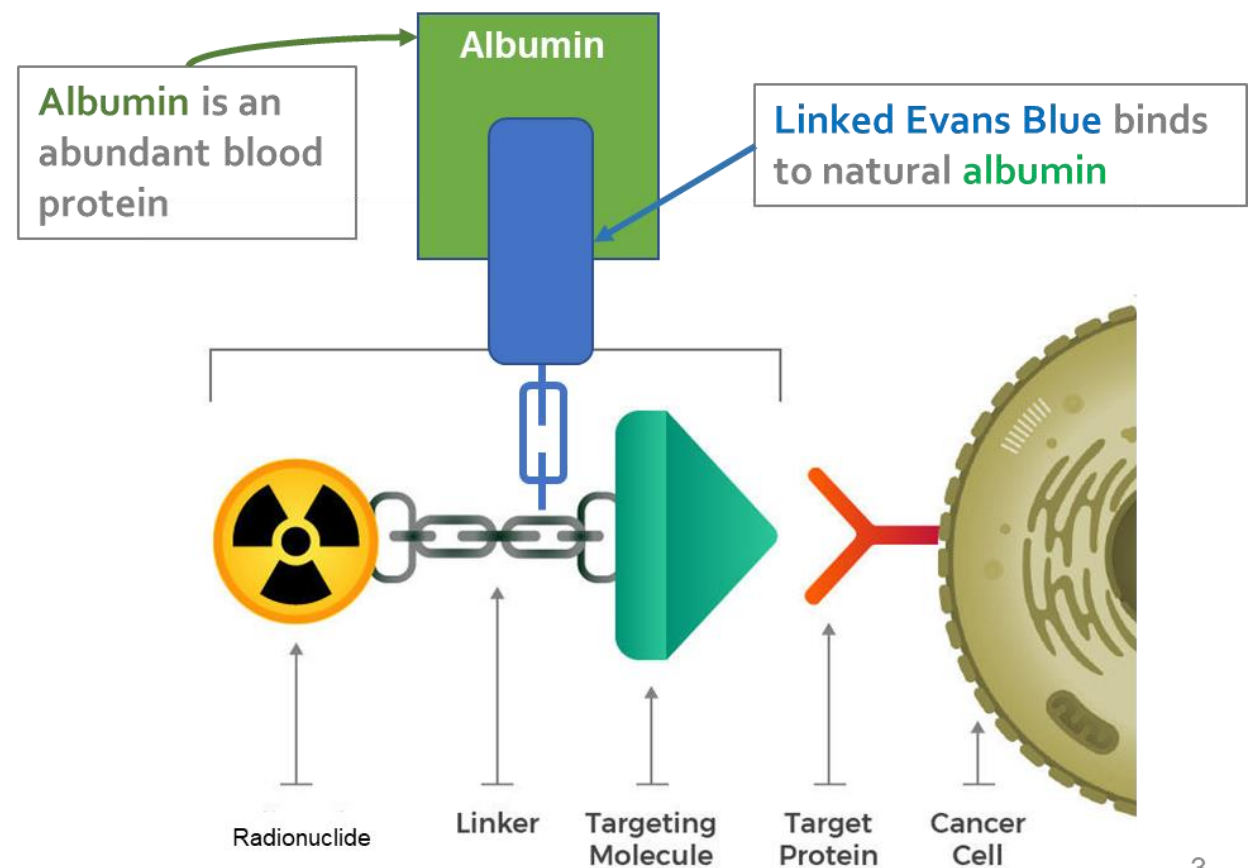
A long-acting, more effective TRT platform

TRTs like Lutathera have short biologic half-lives, limiting efficacy



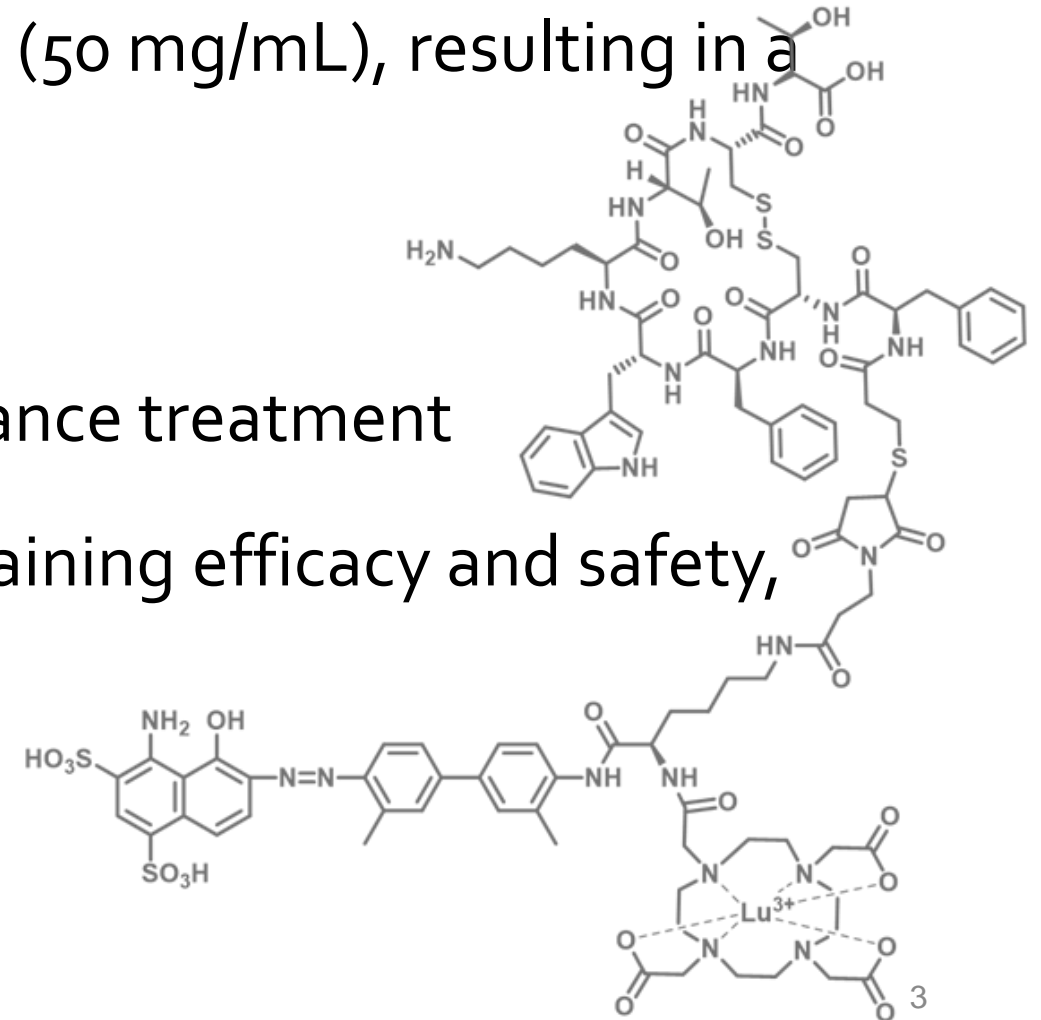
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Evans blue (EB) – extends blood half-life increasing tumor uptake, improving efficacy.



Transforming radiotherapy with an Evans blue (EB) moiety

- EB binds to albumin, abundant in the blood (50 mg/mL), resulting in a longer circulatory half-life
- Each albumin binds 8-14 molecules of EB
- Better tissue absorption and retention enhance treatment
- Significantly lower isotope use while maintaining efficacy and safety, improves costs and health economics



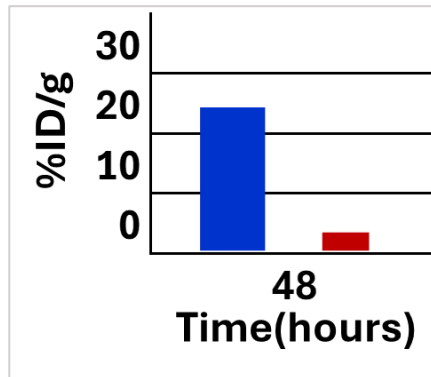
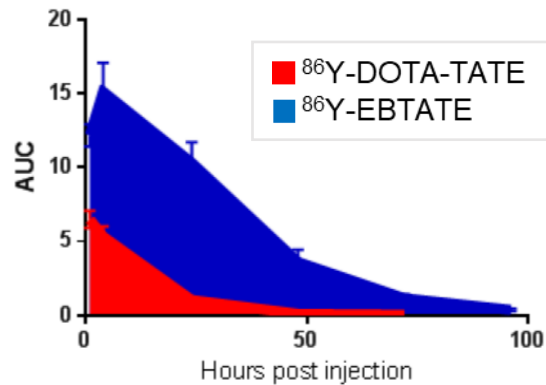
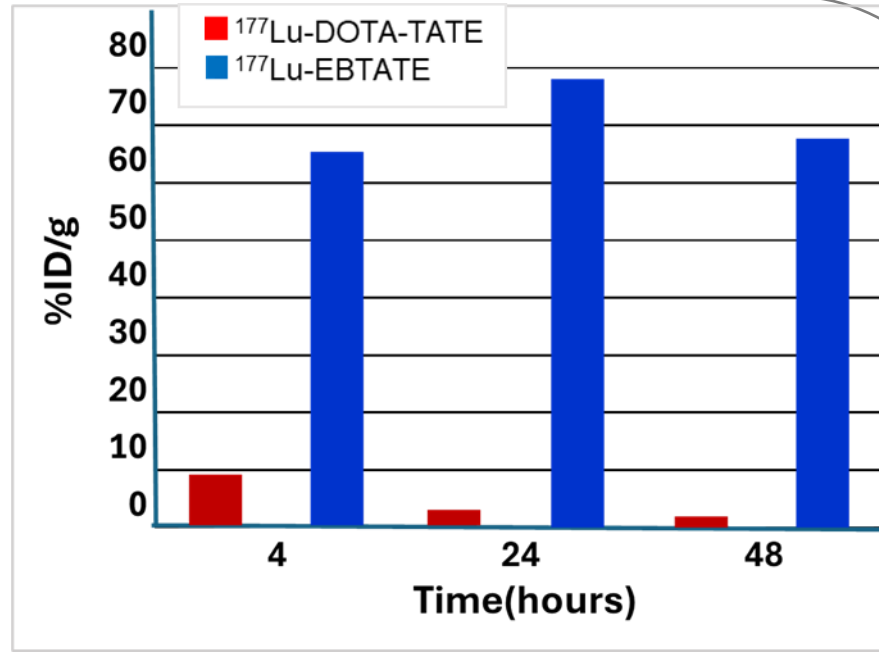
Evans blue (EB) Advantages - transforming radiotherapy

	¹⁷⁷ Lu-EBTATE	vs. ¹⁷⁷ Lu-DOTA-TATE
Circulatory half-life	Binds to albumin, an abundant blood protein, resulting in a longer half-life	Clears rapidly
Tumor uptake in HCT116 CRC tumor model at 24H	78.8% ID/g	3% ID/g
Tumor retention in NET patients	0.049MBq-h/MBq/g 8 Fold greater!	0.0059 MBq-h/MBq/g
Tumor remission in AR42J pancreatic cancer tumor model	Complete	None

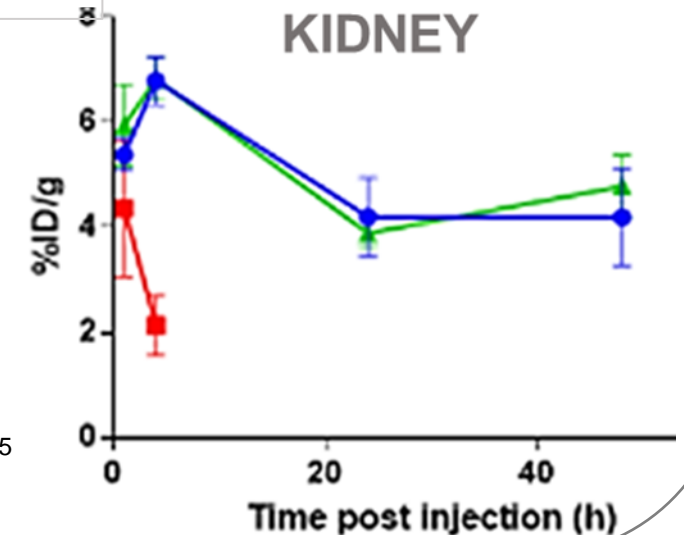
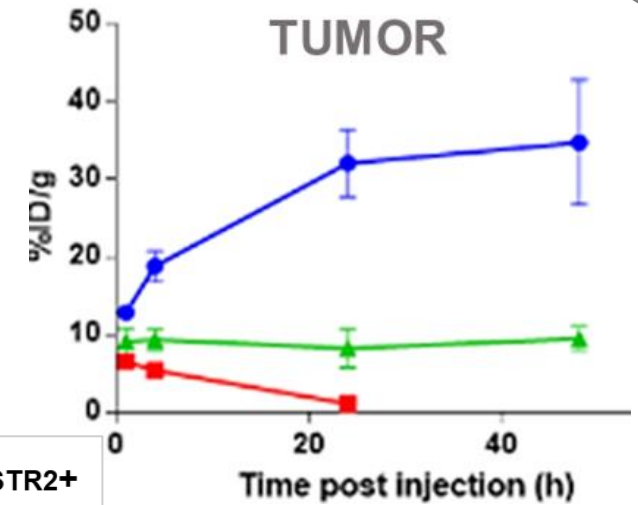
EB impact: Greater retention in HCT₁₁₆ CRC tumor (Preclinical)

^{177}Lu -EBTATE (78.8% ID/g) vs ^{177}Lu -DOTA-TATE (3% ID/g) at 24 h

SSTR2+
tumor



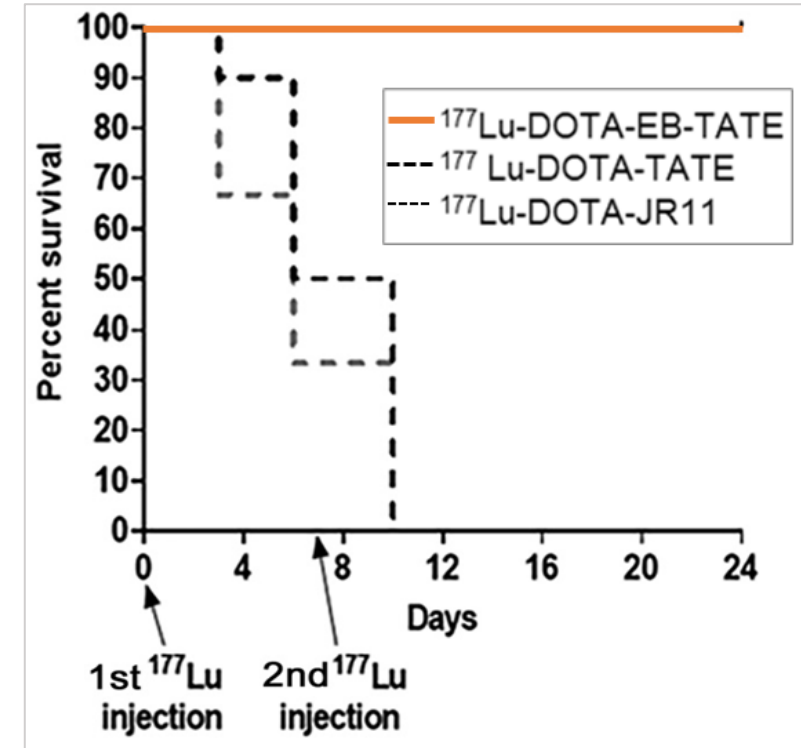
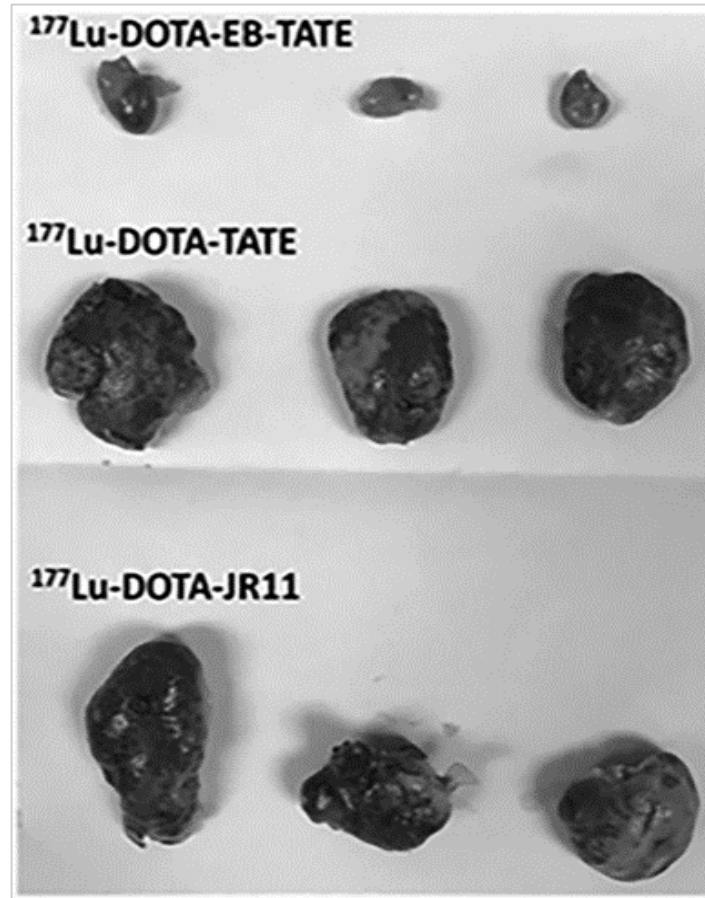
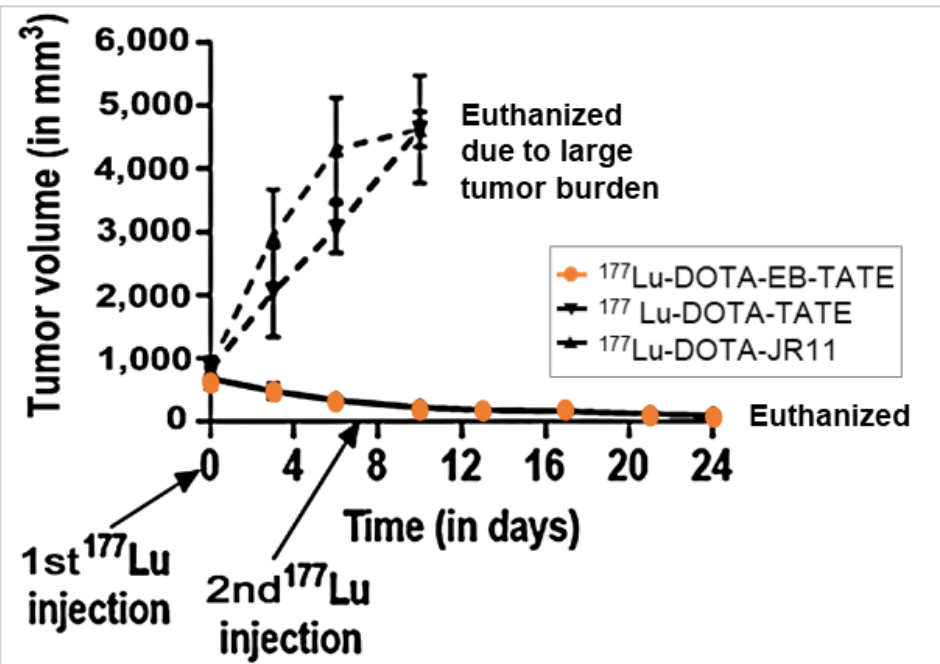
SSTR2 +/-
tumor



Theranostics 2018; 8: 734-745

EB impact: Improved survival in AR42J, pancreatic cancer (Preclinical)

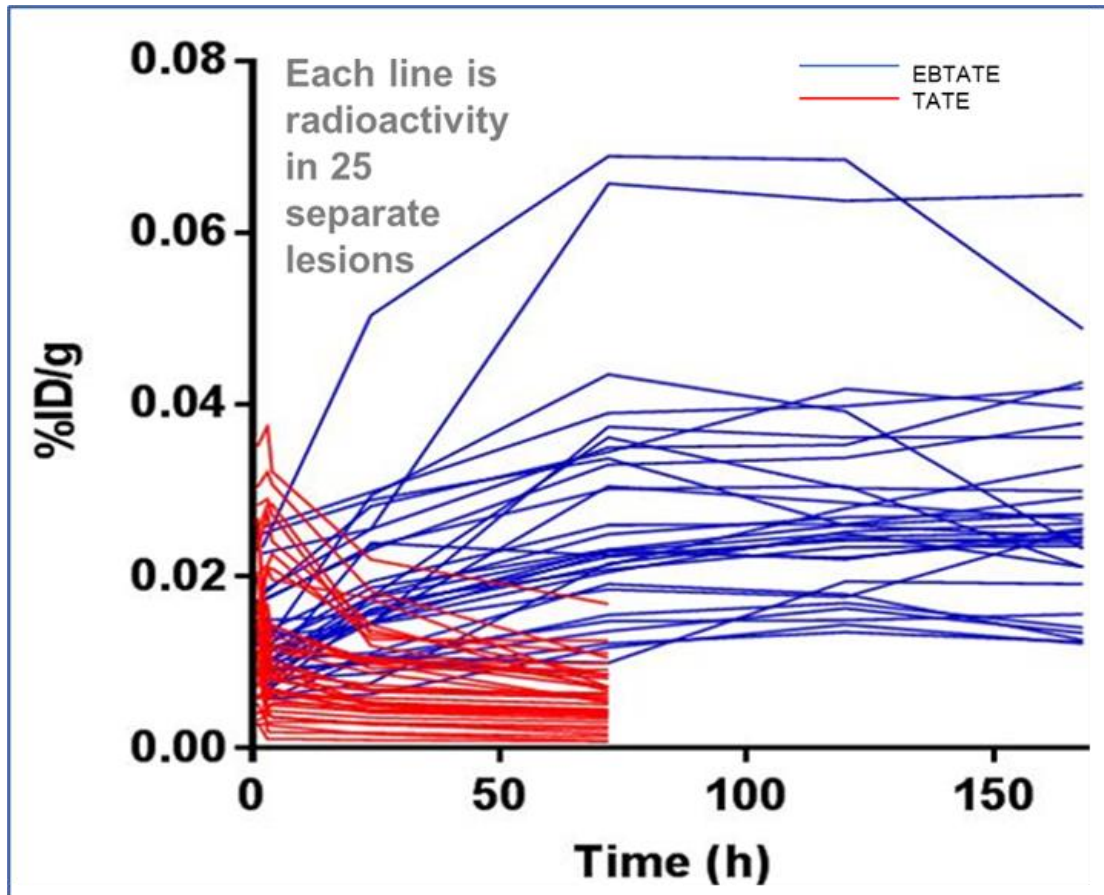
^{177}Lu -EBTATE (complete tumor remission) vs. TATE analogs (no remission)



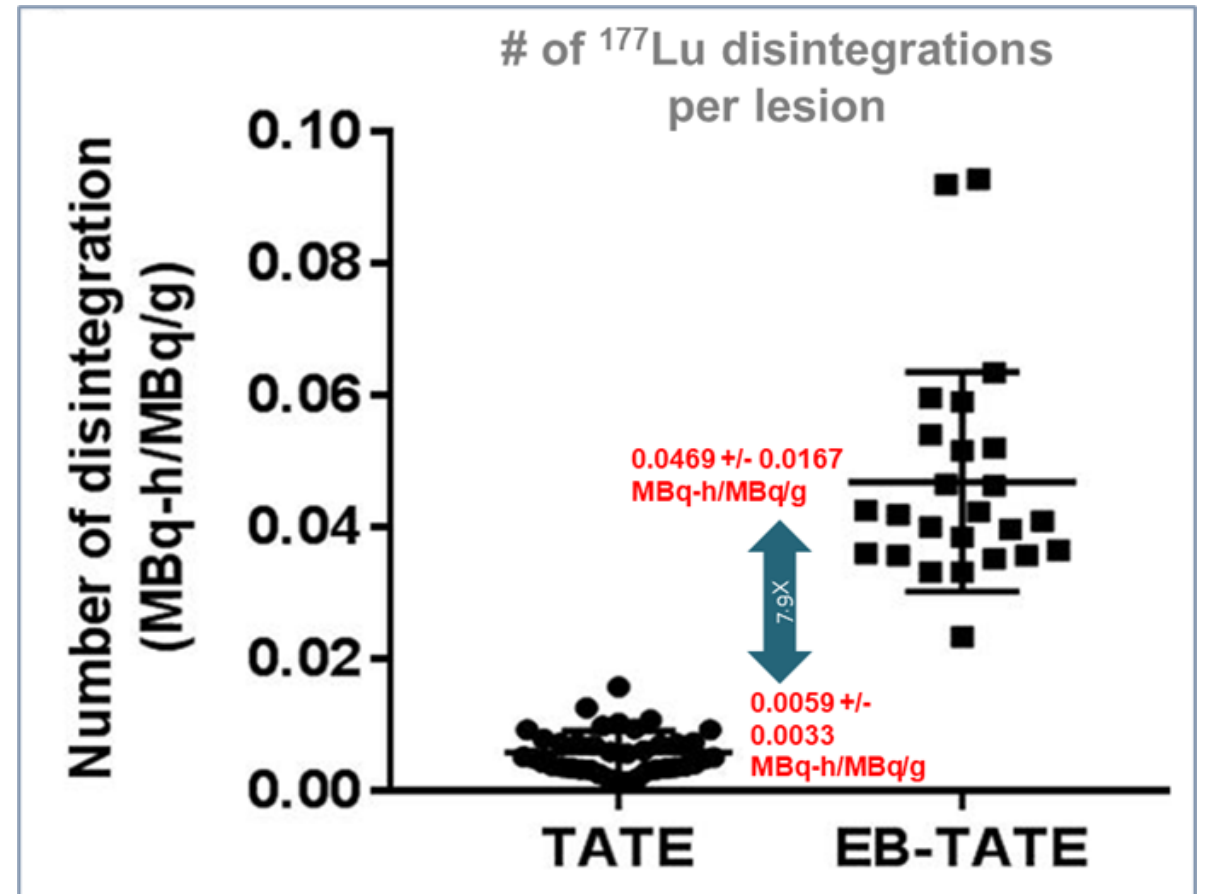
DOTA-EB-TATE is superior to other somatostatin analogues in the treatment of SSTR2-expressing tumors

EB improves PK/PD in patients

EBTATE sustained tumor absorption in NET patients



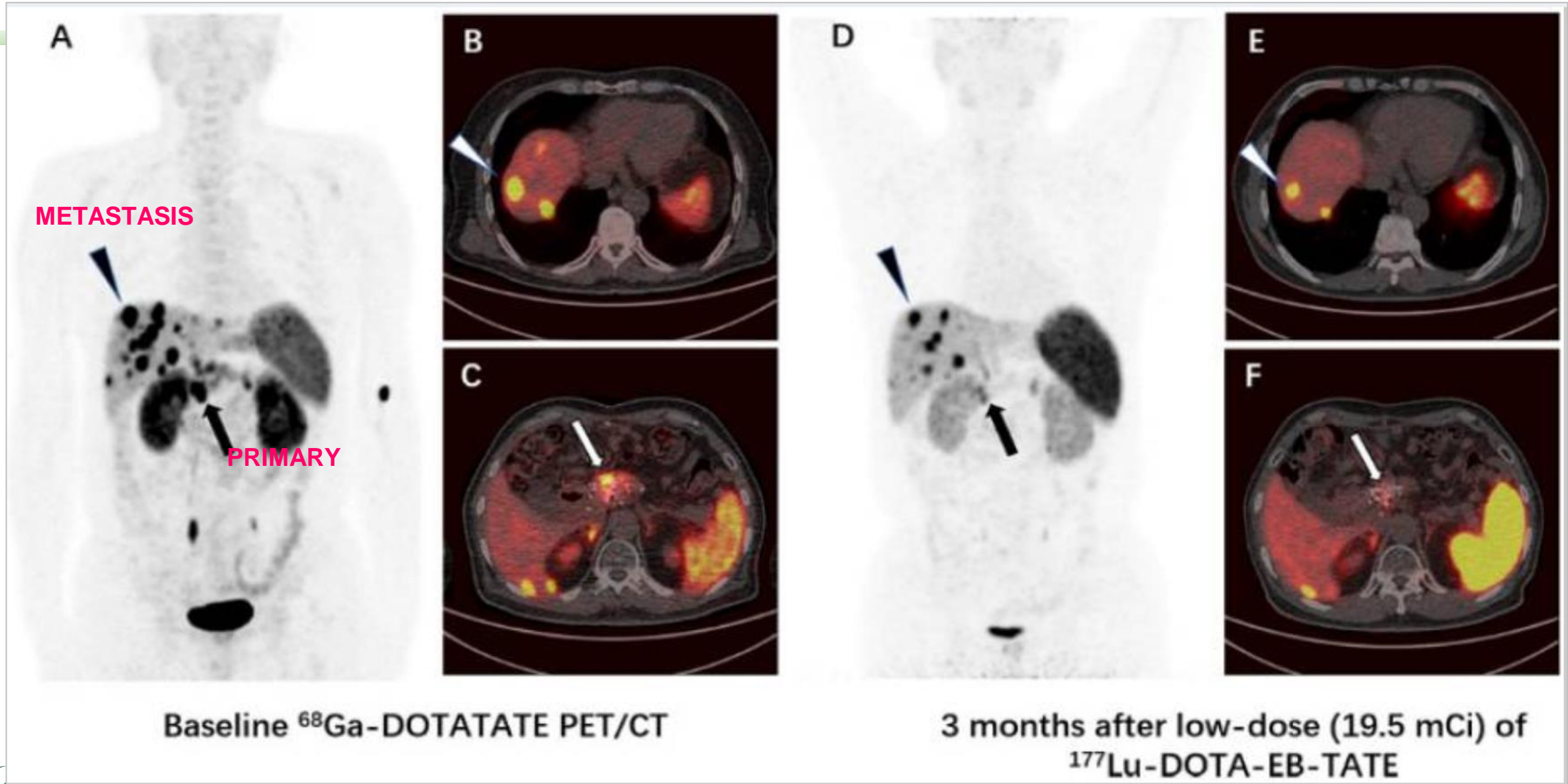
EBTATE shows a 7.9-fold tumor radiation count increase vs ^{177}Lu -DOTA-TATE



EB Platform - targeting unmet medical needs

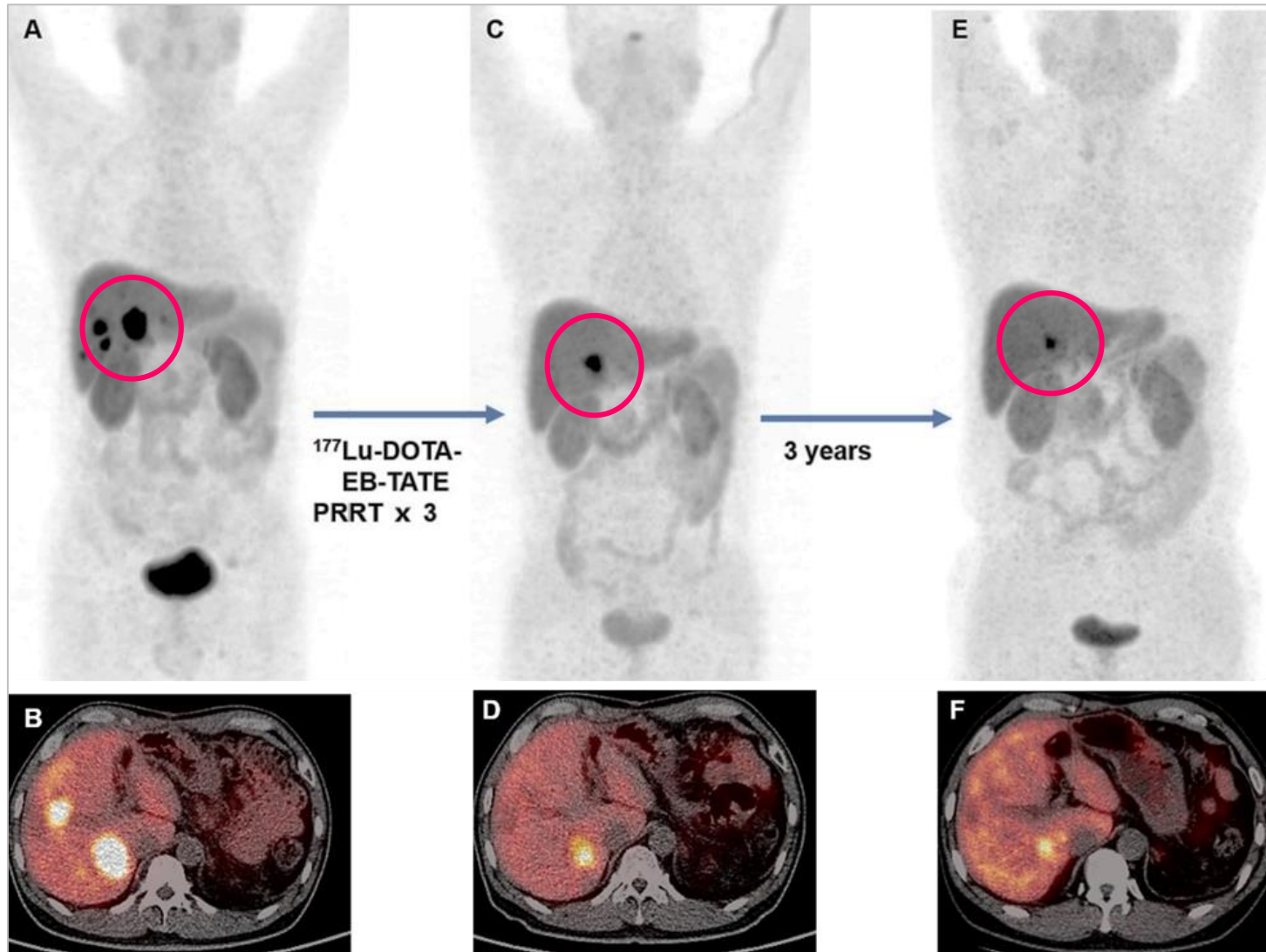
DRUG	TARGET RECEPTOR	INDICATIONS	DEVELOPMENT STAGE	MARKET POTENTIAL
EBTATE[®] ¹⁷⁷ Lu-EB-DOTA-TATE	Somatostatin receptor type 2 (SSTR2)	GEP-NET	Preclinical studies showed superiority over other SSTR2 targeting PRRTs 60+ patients treated. Proved safety and efficacy.	Best-in-class potential \$1 Bn ~430,000 cases (global)
		Radioactive iodine-resistant/refractory (RAI-R) & Hürthle cell (HTC) thyroid cancers	Approved for Phase I/II	\$500M ~140,000 cases (global)
		Nasopharyngeal cancer (NPC)	Approved for Phase I/II	\$500M ~130,000 cases (primarily SE Asia)
		Small cell lung cancer	Ready for Phase I	\$500M ~164,000 cases (global)
²²⁵ Ac-EB-DOTA-TATE	SSTR2	GEP-NET	Target Phase I in 2025	\$1Bn ~430,000 cases (global)
		Small cell lung cancer		\$500M ~130,000 cases (primarily SE Asia)
EBRGD[™] ¹⁷⁷ Lu-EB-DOTA-RGD	Integrin αvβ3	NSCLC - first in class	Strong preclinical efficacy in NSCLC, GBM & CRC.	\$7Bn ~2M cases (global)
		GBM	Pilot GBM patient study showed robust, focal target engagement	
		Colorectal cancer - first in class		

A single low dose (20 mCi) of EBTATE reduces NET tumor size



Long-Term Efficacy

EBTATE (3 cycles) achieved favorable 3-year follow-up results in 29 NET patients



^{68}Ga -DOTATATE PET/CT diagnostic tracking at 3-year follow-up

Jiang et al. Theranostics 2022; 12(5): 6437-6445

EBTATE was safe and well-tolerated in NET patients

Jiang et al. Theranostics 2022; 12(5): 6437-6445

Low, long-term toxicity (CTCAE 5.0) in 29 patients

Toxicity	CTC-grade	Baseline	1st cycle		2nd cycle		3rd cycle		Avg. Grade 3&4 AE (%)
			2 wks	4 wks	2 wks	4 wks	2 wks	4 wks	
Leukopenia	Grade-1 & 2	4	6	5	6	10	6	4	0%
	Grade-3 & 4	0	0	0	0	0	0	0	
Thrombocytopenia	Grade-1 & 2	0	3	3	2	4	2	3	13%
	Grade-3 & 4	0	0	2	1	1	1	0	
Anemia	Grade-1 & 2	3	6	4	5	5	4	4	3%
	Grade-3 & 4	1	0	1	0	0	0	0	
Nephrotoxicity	Grade-1 & 2	7	1	2	1	1	1	0	0%
	Grade-3 & 4	0	0	0	0	0	0	0	
Hepatotoxicity	Grade-1 & 2	5	1	3	2	1	1	0	3%
	Grade-3 & 4	0	0	1	0	0	0	0	

EBTATE Clinical Benefits

safe & effective at 40% radiation exposure

CLINICAL BENEFIT	¹⁷⁷ Lu-EBTATE	vs.	¹⁷⁷ Lu-DOTA-TATE*
Lower cumulative radiation exposure	Cumulative 11.1 GBq		Cumulative 29.6 GBq
Fewer doses	3 cycles x 100mCi		4 cycles x 200mCi
Higher ORR	43-50%		43%
Comparable disease control	86.1% after 3Y		79.4-88%
Stronger IP	Composition of matter to 2037		Formulation patent
Toxicity/admin burden	Doesn't require amino acid pretreatment		Mandated amino acid pretreatment

* Lutathera plus octreotide LAR. Earlier Lutathera monotherapy studies demonstrated ORR of 13-19%. EBTATE shown here is monotherapy

Long acting [^{225}Ac]Ac-EBTATE is highly efficacious against somatostatin receptor-2-positive neuroendocrine tumors

- Two doses of ^{225}Ac -EBTATE at 34 kBq, 10 d apart, were well tolerated biochemically and hematologically for 28 d
- ^{225}Ac -EBTATE (2x 30 kBq, 10 d apart), in NCH-H524 [small cell lung cancer] showed 80% complete remission, 100% survival (d83) and 105.6% TGI, 2-fold more than ^{225}Ac -DOTATATE on d20
- ^{225}Ac -EBTATE (2x 30 kBq, 10 d apart) in NCH-H727 [lung/carcinoid] led to partial responses with 64.4% TGI on d28
- Using 60% less activity of ^{225}Ac -EBTATE is as effective as ^{225}Ac -DOTATATE

EB Platform IP

- “Chemical conjugates of Evans blue derivatives and their use as radiotherapy and imaging agents”
- Approved Countries:
 - US,(US 10,696,631 B2),
 - Europe (EP 3455 206 B1),
 - China (CN 109153641B),
 - Japan (JP6946342B2),
 - Singapore (SG11201809982RA)
- Patent life: 2037
- Licenses: exclusive global license from the National Institutes of Health includes conjugating any new targeting peptides with EB.

EB Summary

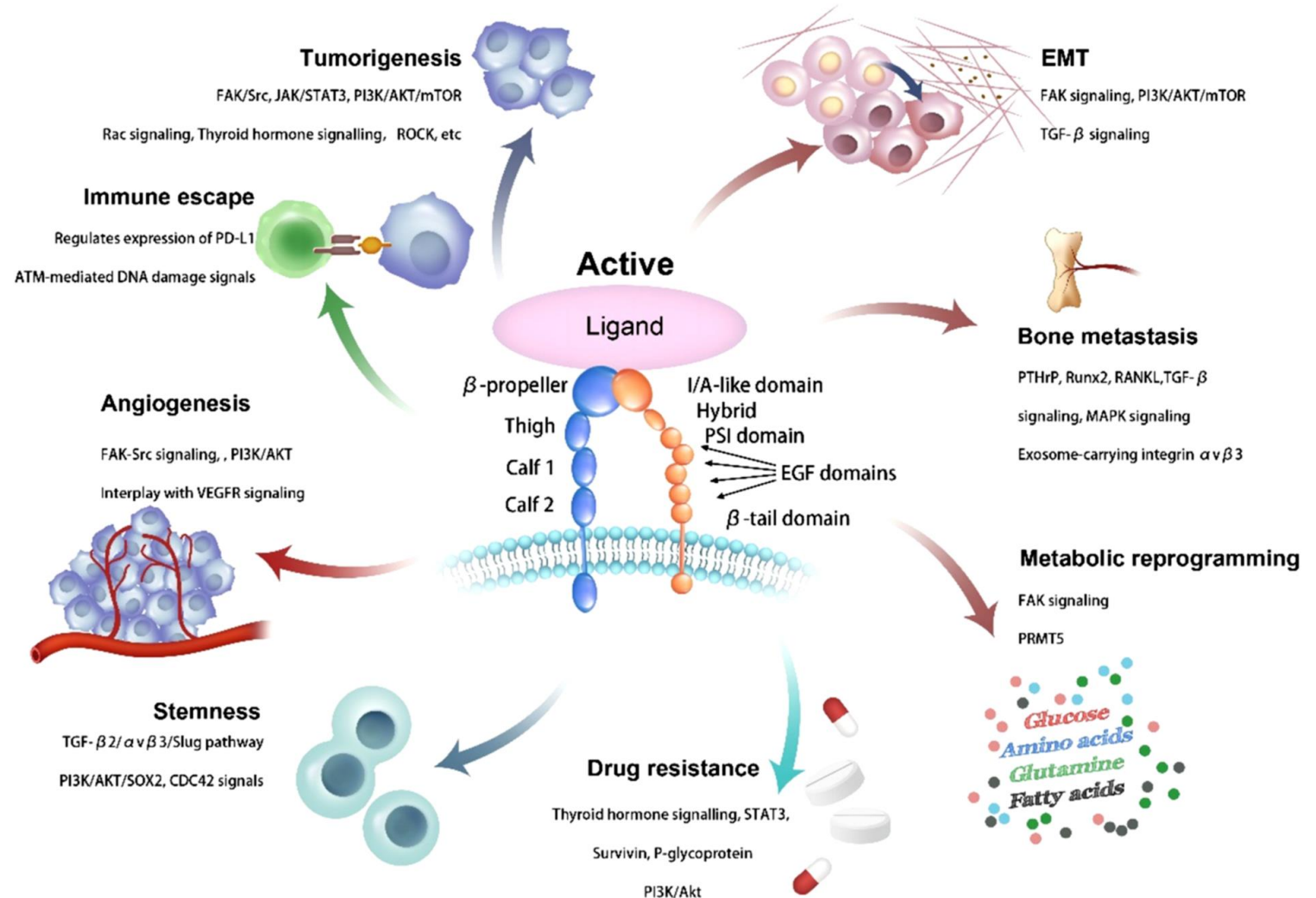
- Transforming radiotherapy with Evans blue(EB)
 - Greater ^{177}Lu -EBTATE uptake
 - Complete remission in AR42J pancreatic model
 - 8-fold greater retention in NET patients
 - Similar safety to ^{177}Lu -DOTATATE with 40% of the radioactivity
- ^{225}Ac -EBTATE showed 80% complete remission, 100% survival and 105.6% TGI, 2-fold more than ^{225}Ac -DOTATATE

EBRGD

EBRGD targets $\alpha v \beta 3$, an integrin with multiple roles in cancer

$\alpha v \beta 3$ in every step of tumor progression:

- tumorigenesis
- epithelial- mesenchymal transition (EMT)
- bone metastasis
- metabolic reprogramming
- drug resistance
- stemness
- angiogenesis
- immune escape



$\alpha v \beta 3$ advantage as cancer target over other integrins

- $\alpha v \beta 3$ has low or no expression in normal tissues
- Expression level increases in tumors and correlates with tumor aggressiveness
 - Some integrins, such as $\alpha 2 \beta 1$, decrease in tumor cells
- $\alpha v \beta 3$ interacts with growth factors highly expressed in tumors
 - $\alpha v \beta 3$ and FGFR interaction induces angiogenesis downstream of FGF binding, and $\alpha v \beta$ s and VEGFR2 promote VEGF-induced angiogenesis
- $\alpha v \beta 3$ is overexpressed in tumors with higher frequency than other integrins

Tumour type	Integrins expressed*	Associated phenotypes
Melanoma	$\alpha v \beta 3$ and $\alpha 5 \beta 1$	Vertical growth phase ^{35,172-174} and lymph node metastasis ^{173,175}
Breast	$\alpha 6 \beta 4$ and $\alpha v \beta 3$	Increased tumour size and grade ¹⁷⁶ , and decreased survival ¹⁷⁷ ($\alpha 6 \beta 4$). Increased bone metastasis ^{36-38,64} ($\alpha v \beta 3$)
Prostate	$\alpha v \beta 3$	Increased bone metastasis ³⁹
Pancreatic	$\alpha v \beta 3$	Lymph node metastasis ⁴⁰
Ovarian	$\alpha 4 \beta 1$ and $\alpha v \beta 3$	Increased peritoneal metastasis ¹⁷⁸ ($\alpha 4 \beta 1$) and tumour proliferation ¹⁷⁹ ($\alpha v \beta 3$)
Cervical	$\alpha v \beta 3$ and $\alpha v \beta 6$	Decreased patient survival ^{41,180}
Glioblastoma	$\alpha v \beta 3$ and $\alpha v \beta 5$	Both are expressed at the tumour-normal tissue margin and have a possible role in invasion ¹⁸¹
Non-small-cell lung carcinoma	$\alpha 5 \beta 1$	Decreased survival in patients with lymph node-negative tumours ¹⁸²
Colon	$\alpha v \beta 6$	Reduced patient survival ¹⁰⁹

* Not a complete list

$\alpha v \beta 3$ integrin is overexpressed in >76% NSCLC patients*

- $\alpha v \beta 3$ expressed in tumor and not in normal cells
- $\alpha v \beta 3$ correlates with tumor grade, progression, metastases and advanced clinical stage

$\alpha v \beta 3$ overexpressed in many cancers

- GBM
- NSCLC
- Breast cancer
- Melanoma
- Sarcoma
- RCC
- SCCHN
- Glioma
- Musculoskeletal cancers
- Rectal Cancer
- Bone metastases

**Boger et al. Virchows Arch. 2014;464(1):69-78.; Echavidre et. al., Pharmaceutics. 2022;14(5):1053;*

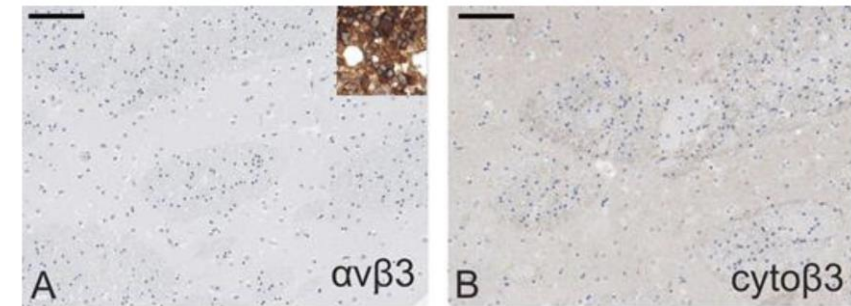
Jin et al. PLoS One. 2012;7(10):e48575, Kariya et. al. Comm Biol 2021;4:490.

$\alpha v \beta 3$ overexpressed in neovascular cells & 60% of GBM patients*

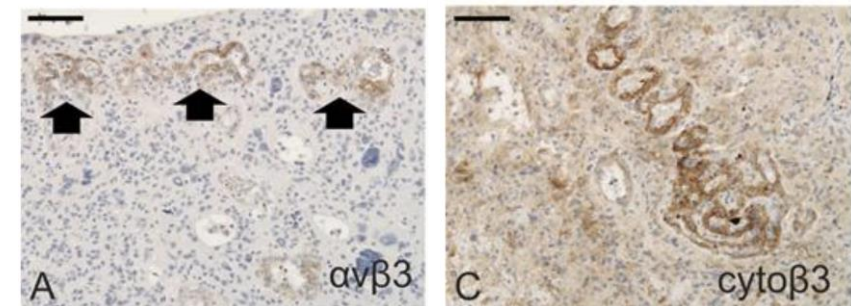
- $\alpha v \beta 3$ integrin has – **low or no expression in normal tissues, overexpressed in many tumors**
- **RGD based PET tracer detects 100% primary lesions in cancer**
- $\alpha v \beta 3$ was found in **neovascular cells and tumor cells**

Brain Pathology 2008;18:378; Theranostics 2016;6:78,
J Neuropath Exp Neur 2013;72:194

$\alpha v \beta 3$ has low/no expression in normal human brain samples



$\alpha v \beta 3$ has elevated expression in GBM tumor vessels and parenchymal region



	$\alpha v \beta 3$ positive tissues
Normal brain	0/78
Glioblastoma (WHO IV)	86/160

*Schittenhelm 2013, Echavidre 2022

Clinical development targeting $\alpha v \beta 3$

Merck KGaA spent >10 years developing a targeted therapy for $\alpha v \beta 3$ in GBM

- Cilengitide, a peptide $\alpha v \beta 3$ antagonist, failed in a Phase 3 GBM trial
- Although safe, cilengitide did not improve overall survival
- Proposed rationale for the failure:
 - Signaling based therapy is not potent enough to kill cancer cells
 - Short residence time is insufficient

EBRGD may overcome these challenges.

Clinical development targeting $\alpha\nu\beta_3$

Novartis began a Phase I trial with an $\alpha\nu\beta_3$ and $\alpha\nu\beta_5$ dual targeting TRT (116 pts)

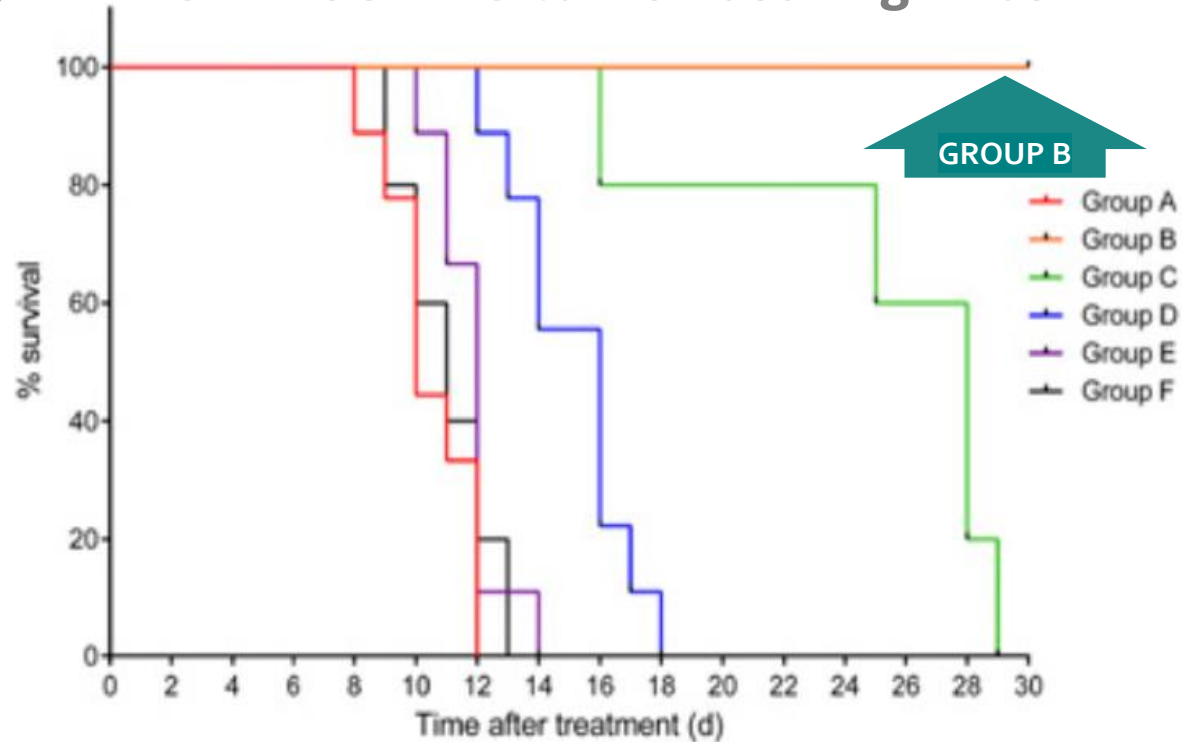
- A Phase I, Open-label, Multi-center Study to Evaluate the Safety, Tolerability, Dosimetry and Preliminary Activity of [^{177}Lu]Lu-FF58 in Patients (N=116) With Selected Advanced Solid Tumors (NCT05977322)
- FF58 is an $\alpha\nu\beta_3$ and $\alpha\nu\beta_5$ dual targeting molecule without the albumin binding motif

MTTI demonstrated RGD without Evans blue is ineffective in tumor control while EBRGD is effective in preclinical models.

EB Impact: Improved survival in GBM and NSCLC (Preclinical)

^{177}Lu & ^{90}Y EBRGD vs. RGD analogs

GBM U87MG tumor bearing mice



Group A: : saline

Group B: ^{90}Y -EBRGD (2x 7.4 MBq)

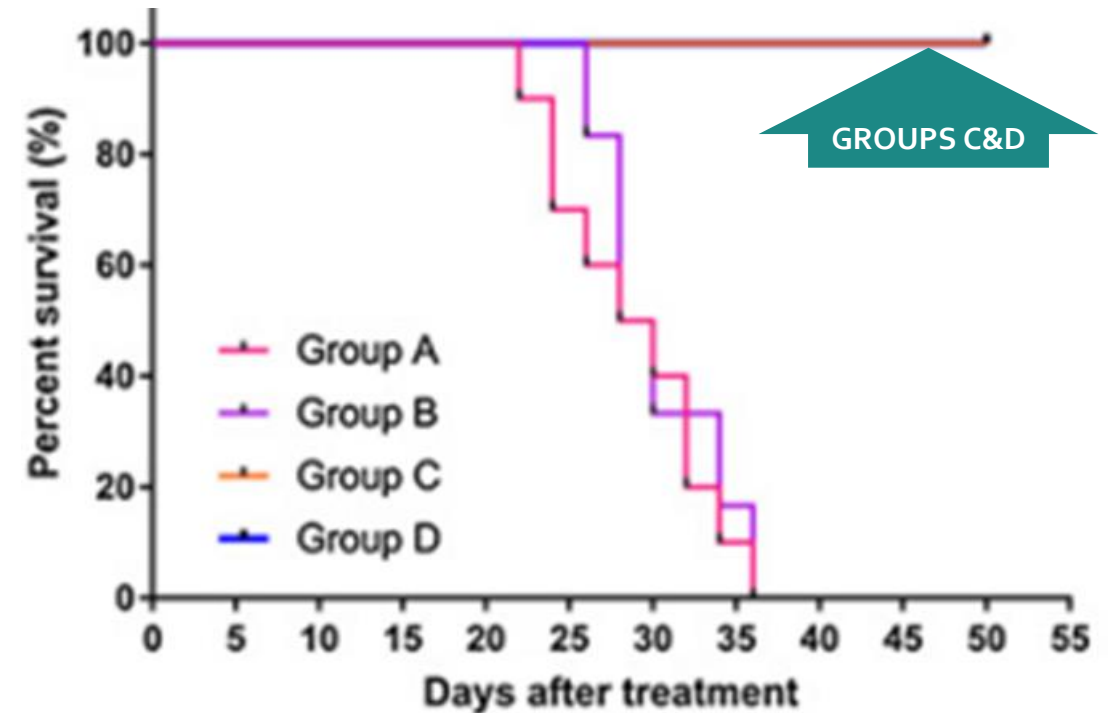
Group C: ^{90}Y -EBRGD (2x 3.7 MBq)

Group D: ^{90}Y -EBRGD (1x 1.85 MBq)

Group E: ^{90}Y -RGD (1x 7.4 MBq)

Group F: ^{90}Y -RGD (1x 1.85 MBq)

NSCLC-PDX BALB/c nude mice



Group A: : saline

Group B: ^{177}Lu -RGD (29.6mBq)

Group C: ^{177}Lu -EBRGD (18.5mBq)

Group D: ^{177}Lu -EBRGD (29.6mBq)

EBRGD is designed to overcome $\alpha v \beta 3$ therapy failures

A validated target

- $\alpha v \beta 3$ is required for angiogenesis and tumorigenesis in cancer
- $\alpha v \beta 3$ therapy has been challenging

EBRGD advantage

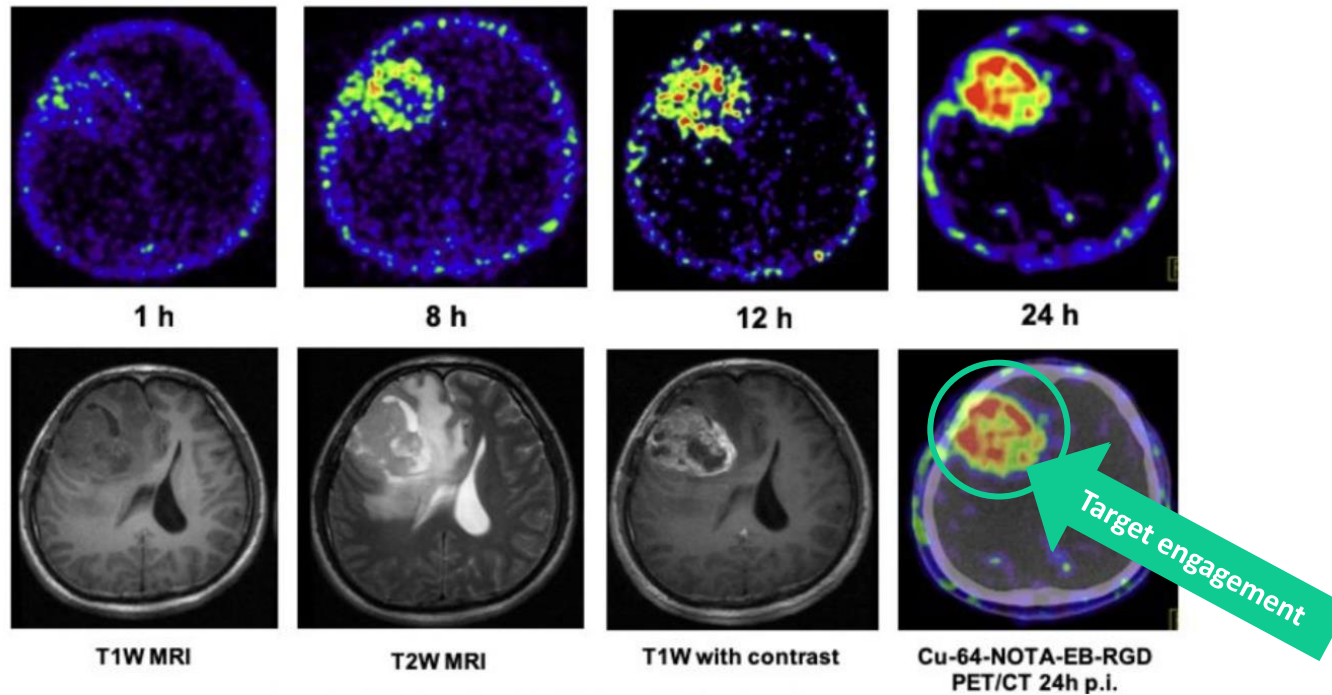
- EBRGD extends *in vivo* circulatory half-life and tumor residence time, enabling effective payload delivery

Strong *in vivo* efficacy

- Convincing efficacy in $\alpha v \beta 3$ positive NSCLC, CRC and GBM model

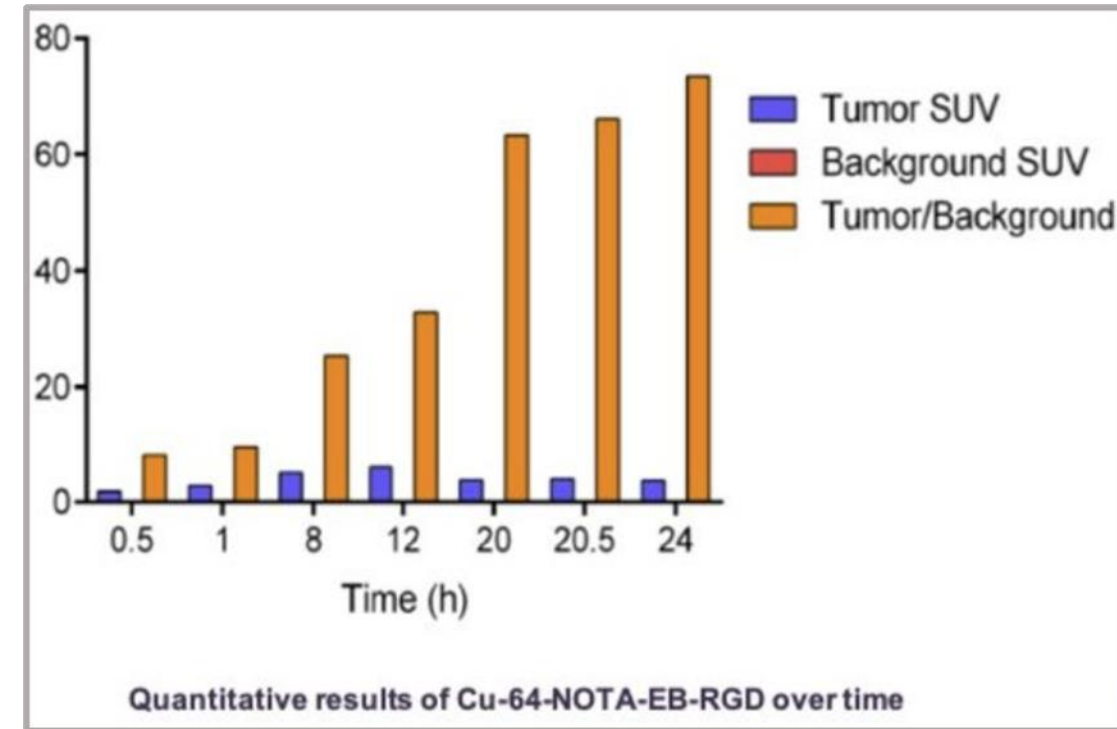
^{64}Cu -EBRGD – robust target engagement in GBM patients

Glioblastoma Multiforme Patient



Axial PET slices of glioblastoma patient injected with ^{64}Cu -EB-RGD at different time points p.i.

Signal/background ratio increased over time



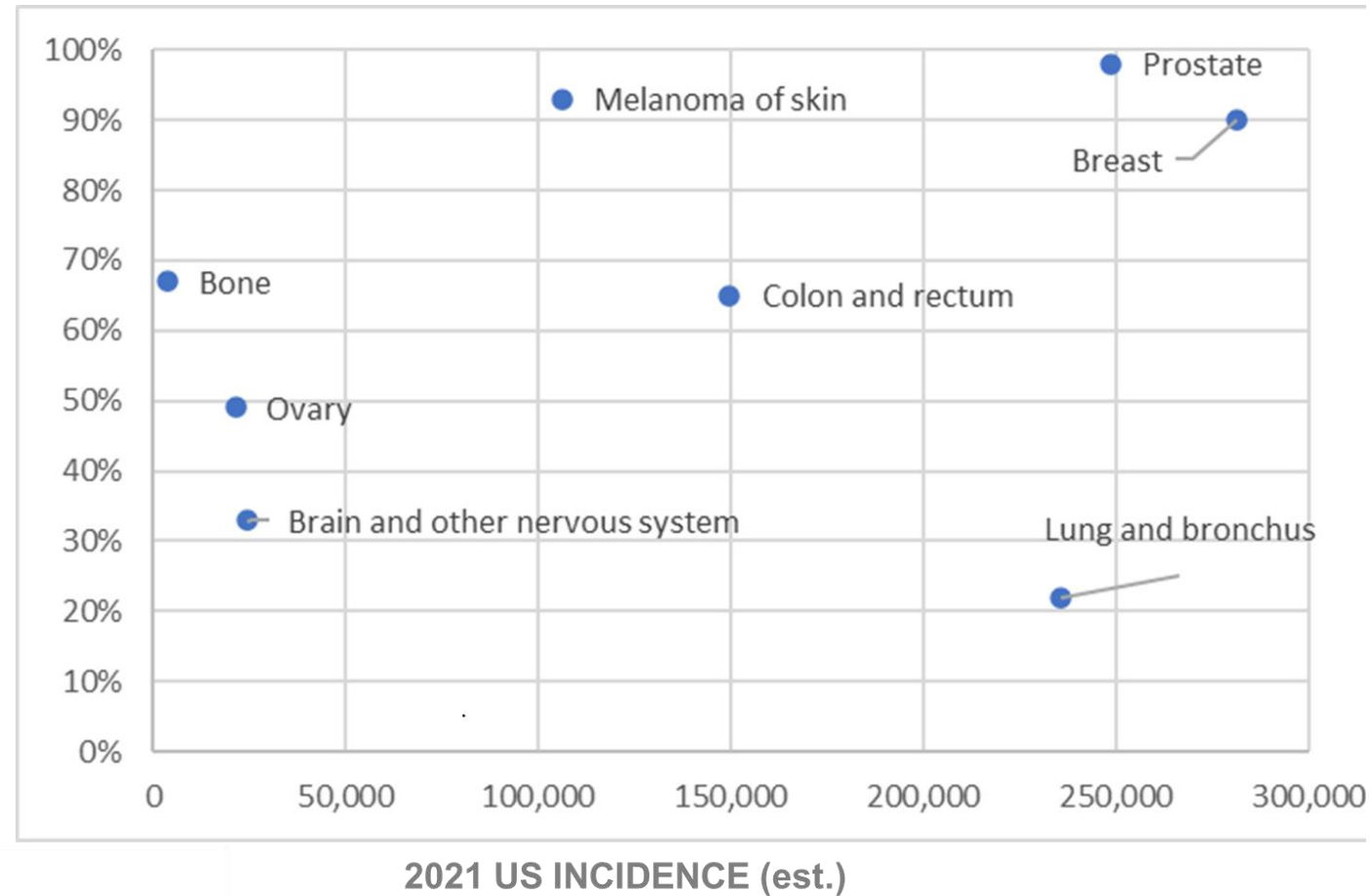
Zhang et al. J Nucl Med 2020; 61(Suppl 1): 349

EBRGD Opportunities

Multiple cancers express Integrin $\alpha_v\beta_3$ therapeutic targets:

- Overexpressed in almost all metastatic cancers
- ~ 1 million US patients annually

5-YEAR
SURVIVAL
2011-2017



Summary

- $\alpha v \beta_3$ is overexpressed in NSCLC, CRC, GBM and many other cancers
- EBRGD demonstrated:
 - ✓ efficacy in NSCLC, CRC and GBM models
 - ✓ tumor eradication in high expressing PDX $\alpha v \beta_3$ +
 - ✓ synergistic effect with immunotherapy
 - ✓ target engagement and sustained tumor absorption in GBM patients

EBRGD IND-enablement update

- Completed GLP toxicology and GMP manufacturing (30,000 doses in cGMP storage)
- Demonstrated acceptable radiolabeling
- Clinical protocols and sites identified for NSCLC and GBM
- Pilot study completed (3 healthy, 2 GBM pts)
- Target IND submission 2025

Pipeline

PRODUCT	TARGET	INDICATION	PRECLIN	PHASE I	PHASE II	PHASE III	MARKET
THERAPEUTICS							
Rabies mAb	Rabies antigen	Rabies	OUTLICENSED - LAUNCHED 2022				
BPRDP056	Phosphatidylserine	Multiple cancers	OUTLICENSED				
¹⁷⁷ Lu-EBTATE [®]	SSTR2	Neuroendocrine tumors	PHASE I/II (n=60 pts)				
	SSTR2	RAI-R & Hürthle Cell thyroid cancers	PHASE I/II				
	SSTR2	Nasopharyngeal cancer	PHASE IB/II				
²²⁵ Ac-EBTATE [®]	SSTR2	Small cell lung cancer	Q1 2025				
	SSTR2	Neuroendocrine tumors	Q2 2025				
¹⁷⁷ Lu-EBRGD [™]	integrin $\alpha v \beta_3$	Non-small cell lung cancer	Q2 2025				
	integrin $\alpha v \beta_3$	Glioblastoma multiforme	PILOT (n=5 pts)		Phase I/II Q2 2025		
DIAGNOSTICS							
TDURA	Cell death	Colorectal cancer	DOSIMETRY (n=6 pts)				
CypH-11 Spray	NIR guided surgery	Colorectal & peritoneal cancers	PHASE I Q3 2025				

MTTI Team

Deep industry experience and record of drug approval



Chris Pak, PhD
- President & CEO



Jeffrey Mattis, PhD,
- SVP Regulatory Affairs



Bryan Gray, PhD,
- SVP Product Development



Jianwei Xu, PhD
- CBO



John Farah, PhD
- Executive Advisor



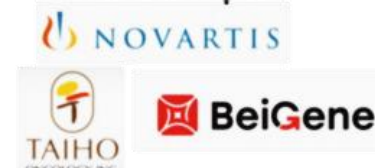
Michael Silvon PhD, MBA
- SVP Business Development



Clinical team/advisors



Jerry Huang, MD PhD - SVP
Clinical Development



Richard Wahl, MD
- Clinical Advisor



Chairman of the Department of Radiology and Director of the Mallinckrodt Institute of Radiology at Washington University School of Medicine



Daniel Pryma, MD
- Clinical Advisor

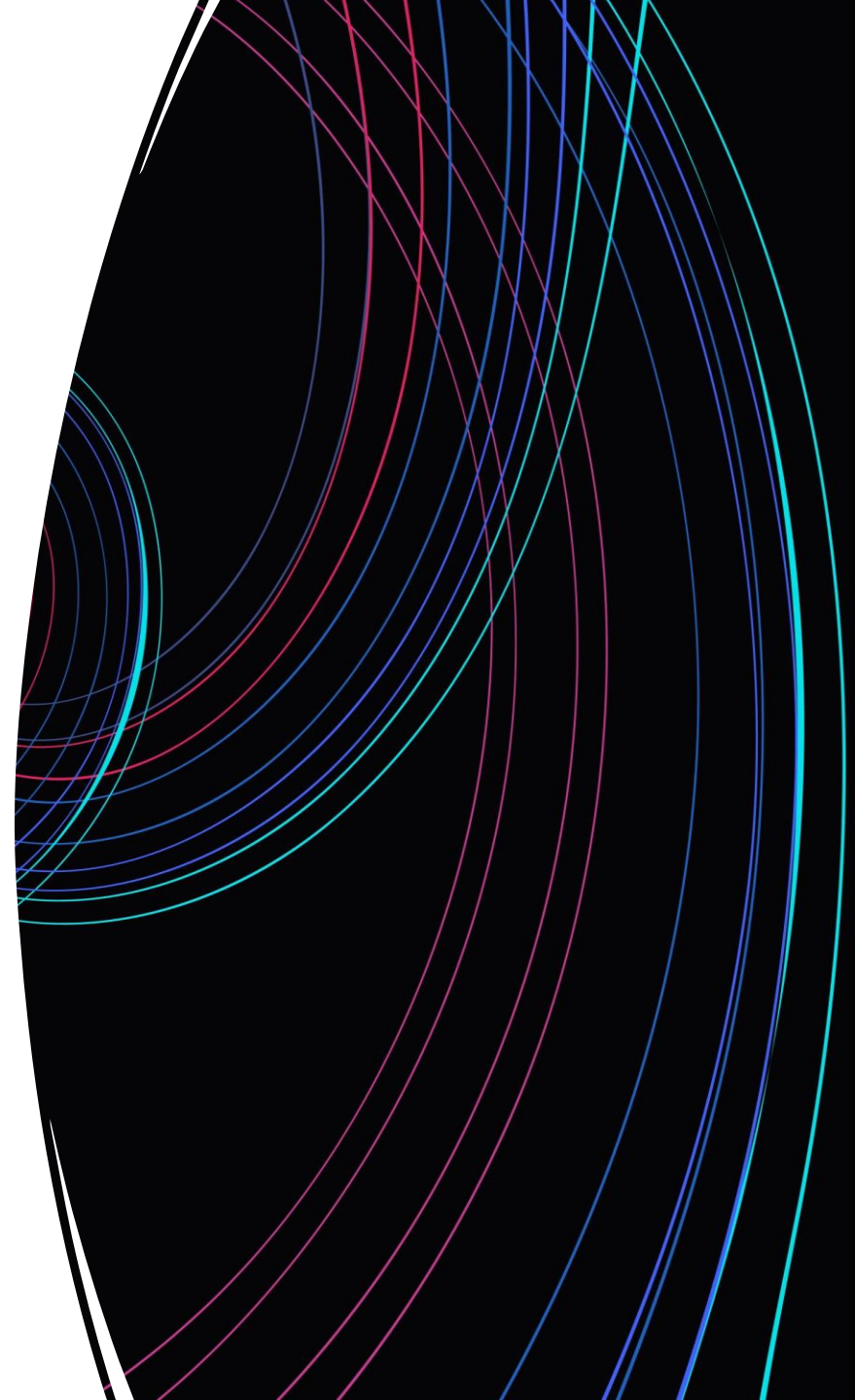


Chief, Division of Nuclear Medicine & Clinical Molecular Imaging

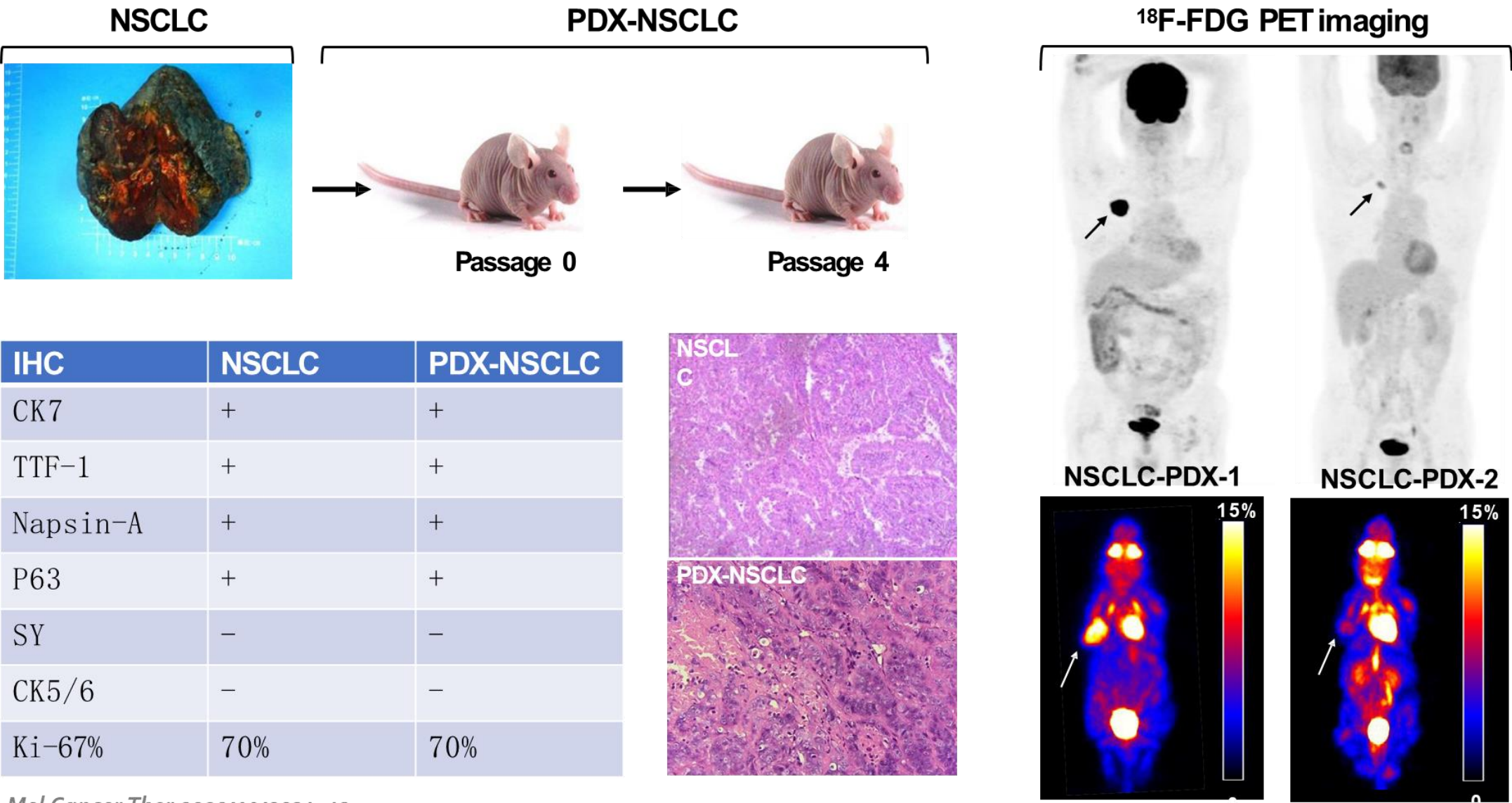
Appendices:

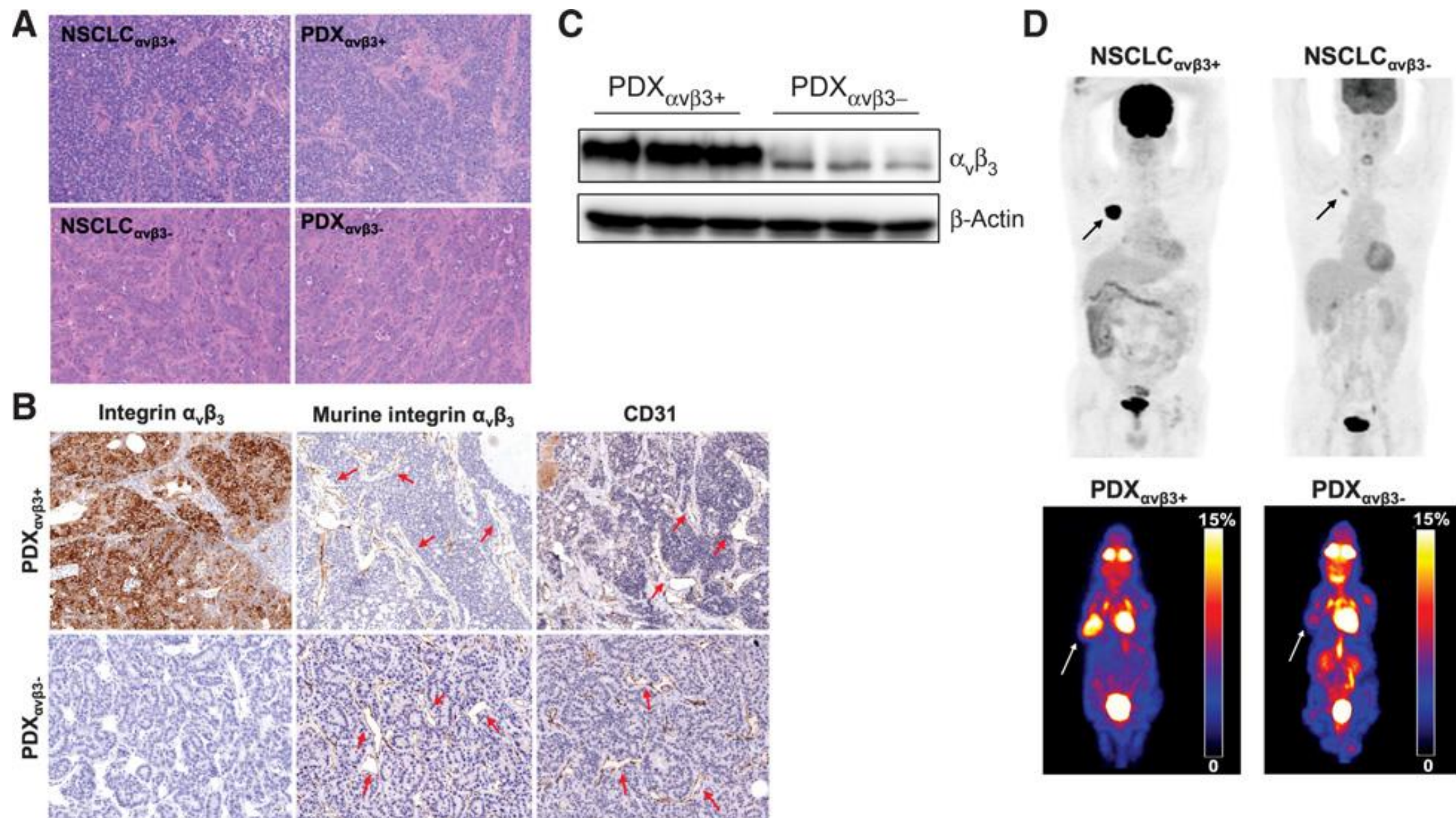
Preclinical studies

- ^{177}Lu -EBRGD
 - NSCLC (PDX)
 - GBM (U87MG)
 - CRC (MC38)
- ^{225}Ac -EBTATE

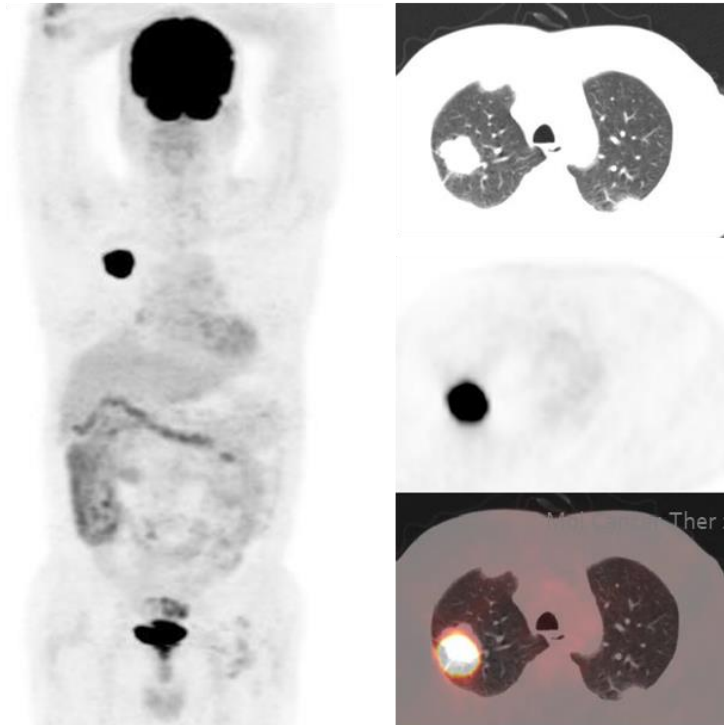


Establishment of patient-derived xenografts in NSCLC (PDX-NSCLC)

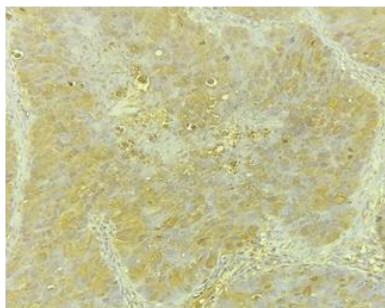




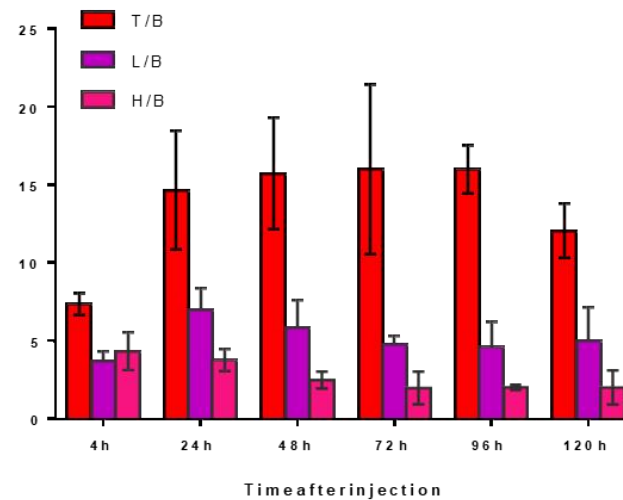
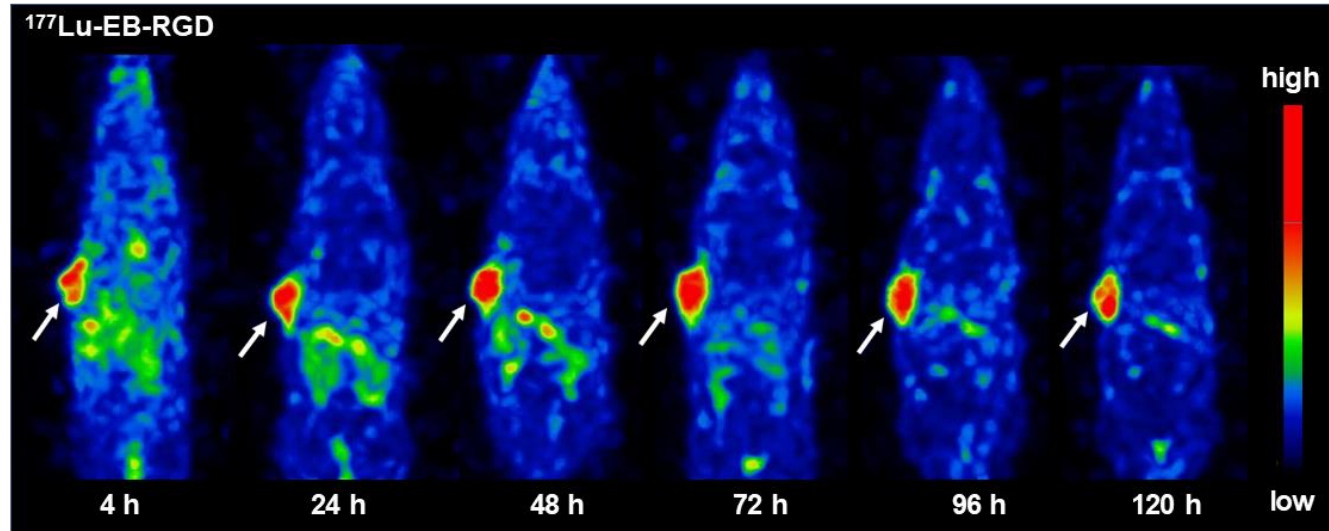
^{177}Lu -EB-RGD SPECT imaging in $\alpha_v\beta_3$ -positive PDX-NSCLC



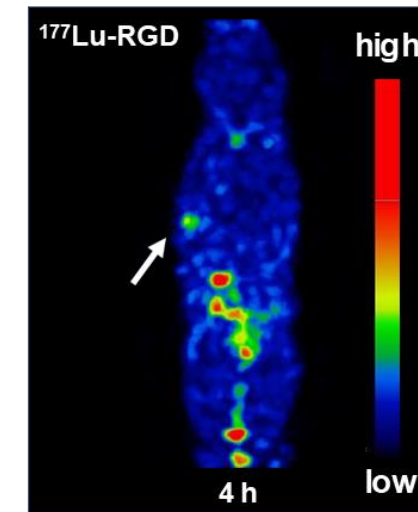
FDG PET imaging in the patient with lung adenocarcinoma, $\alpha_v\beta_3$ high expression



IHC:
 $\alpha_v\beta_3$ high expression



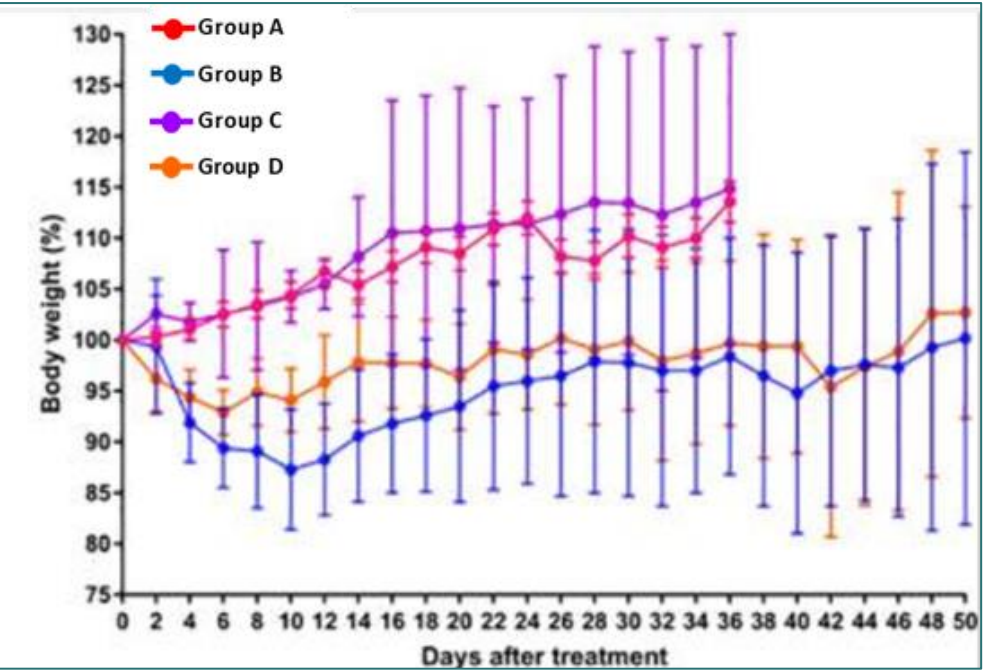
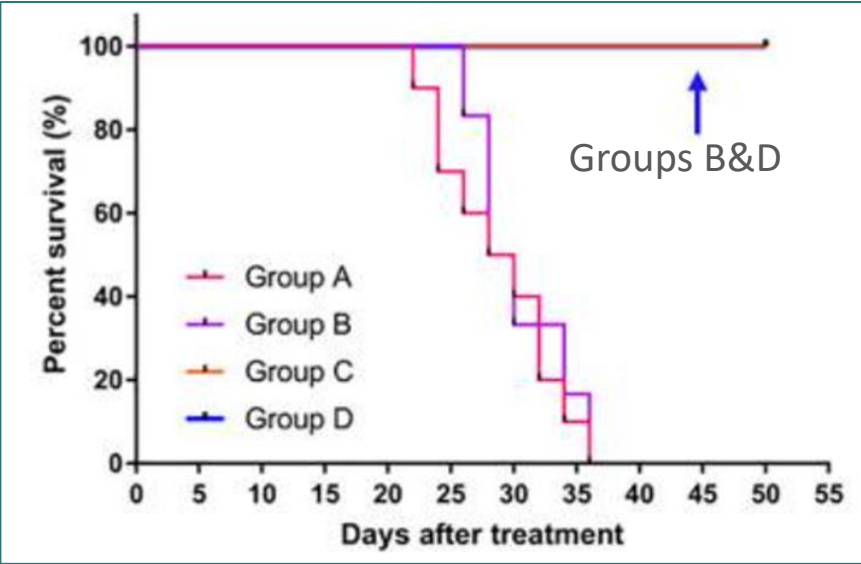
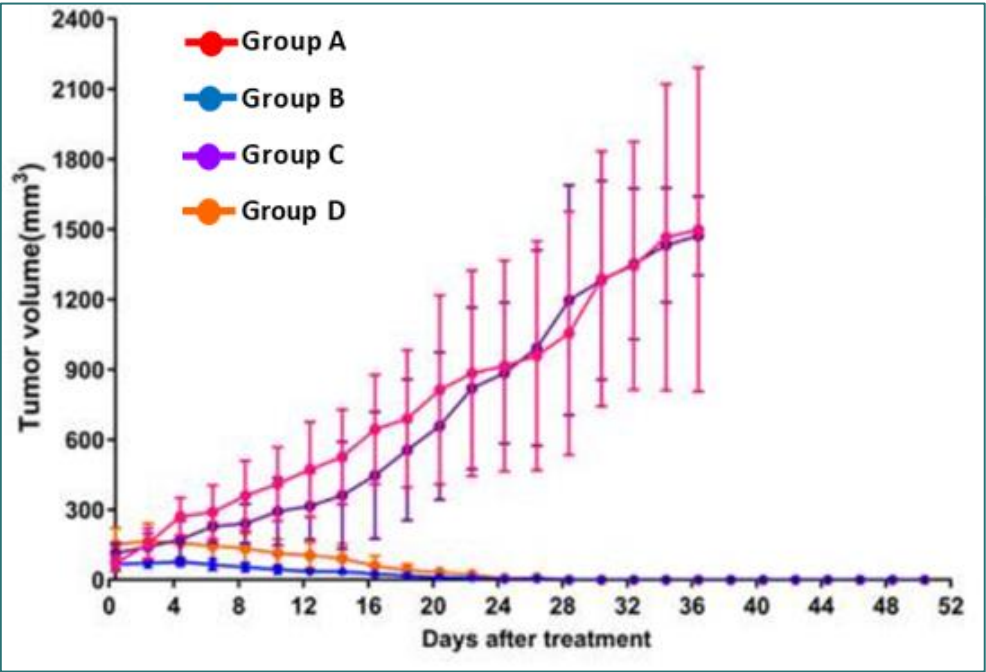
^{177}Lu -EB-RGD vs. ^{177}Lu -RGD SPECT imaging in $\alpha_v\beta_3$ -positive PDX-NSCLC



^{177}Lu -EBRGD resulted in tumor volume regression and improved survival of $\alpha v\beta_3$ + PDX (NSCLC) mice

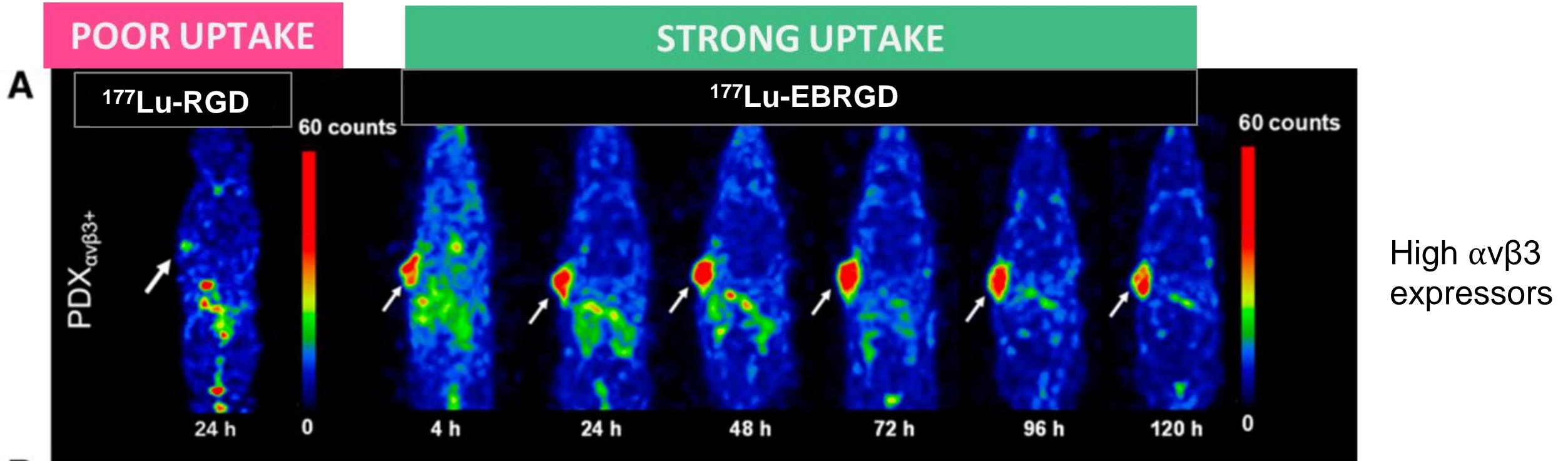
- Day 0 ● Group A: Saline
- Day 0 ● Group B: ^{177}Lu -EB-RGD (18.5 MBq)
- Day 0 ● Group C: ^{177}Lu -RGD (29.6 MBq)
- Day 0 ● Group D: ^{177}Lu -EB-RGD (29.6 MBq)

A single dose of ^{177}Lu -EB-RGD (18.5 MBq) completely eradicated tumors in PDX $\alpha v\beta_3$, with no sign of tumor recurrence during the observation period

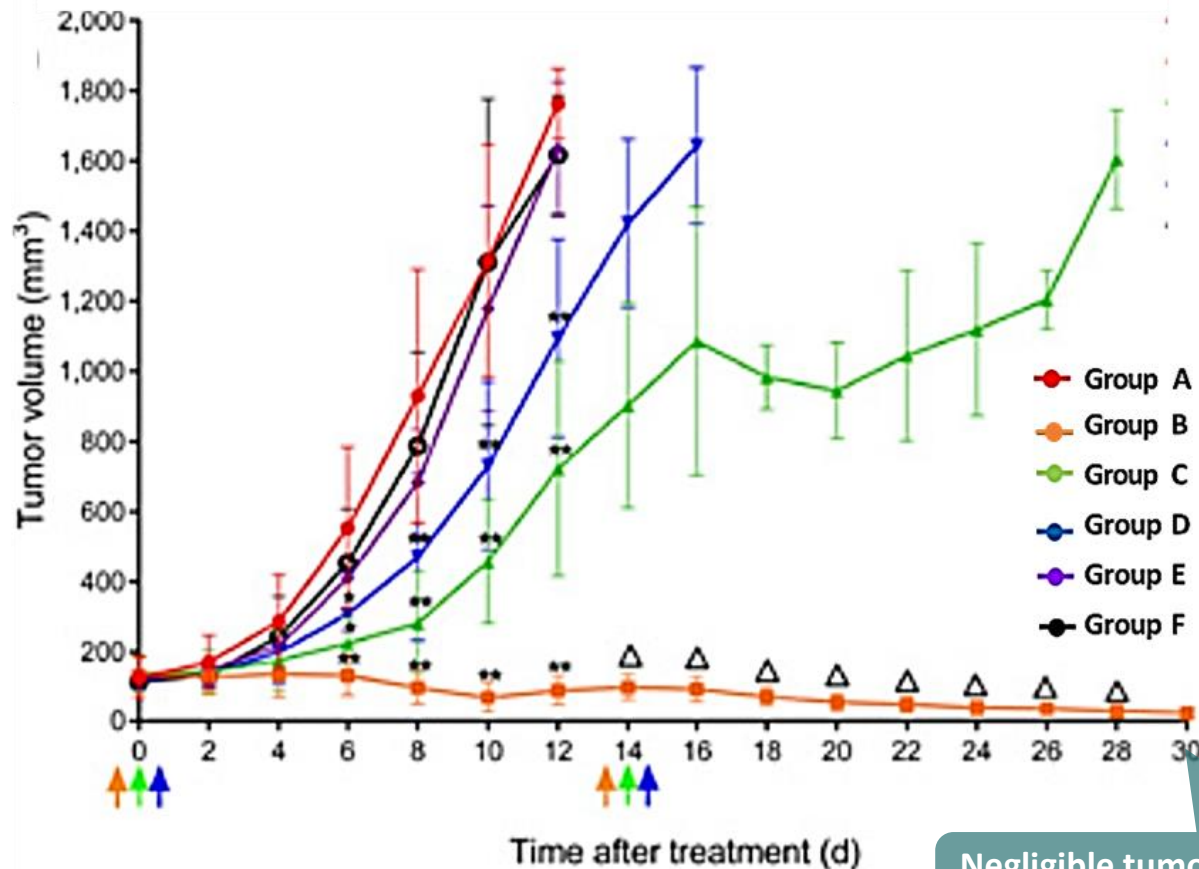


^{177}Lu -EBRGD vs ^{177}Lu -RGD SPECT imaging in $\alpha_v\beta_3$ positive PDX-NSCLC

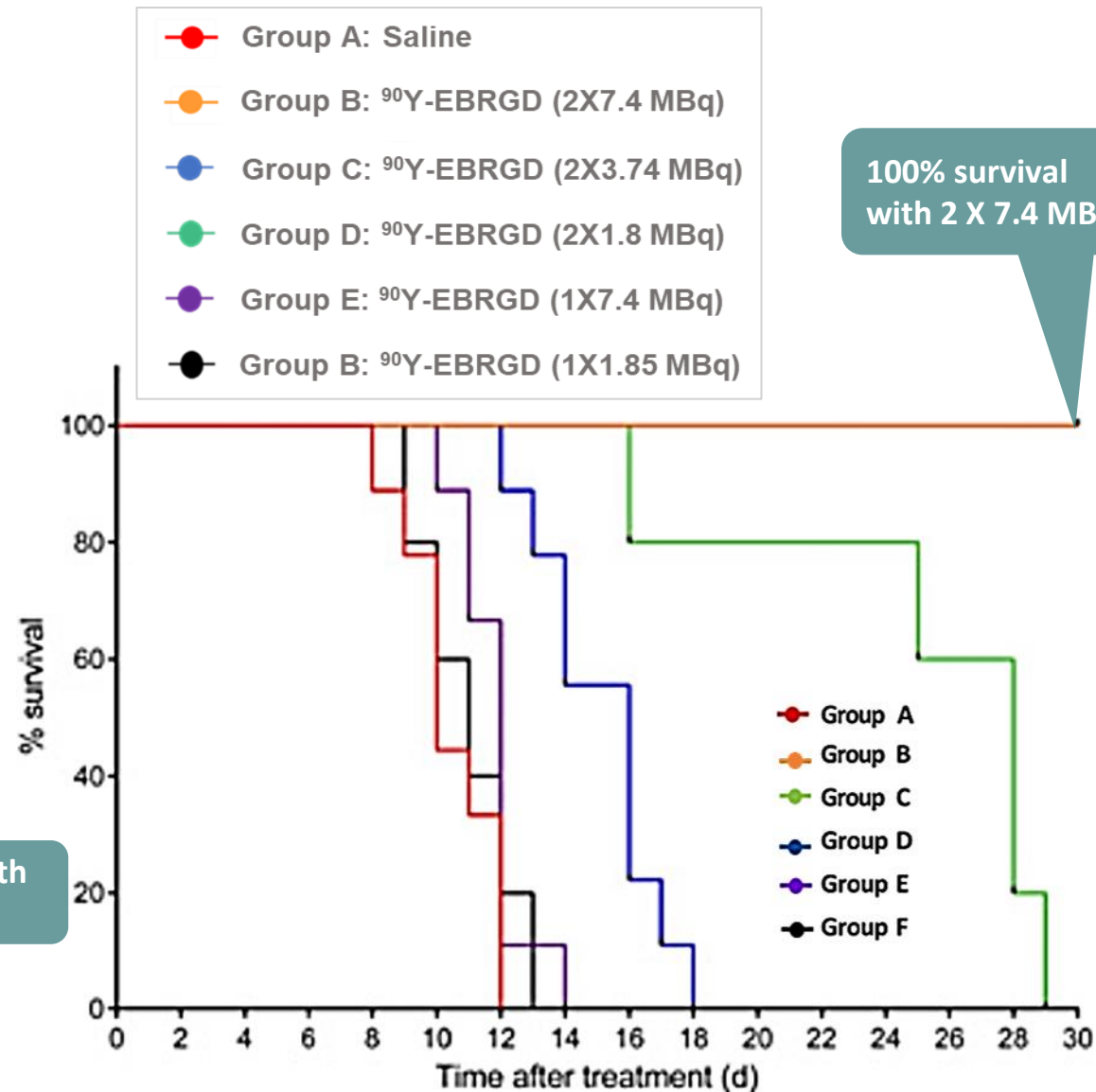
EBRGD's longer residence time significantly improves uptake



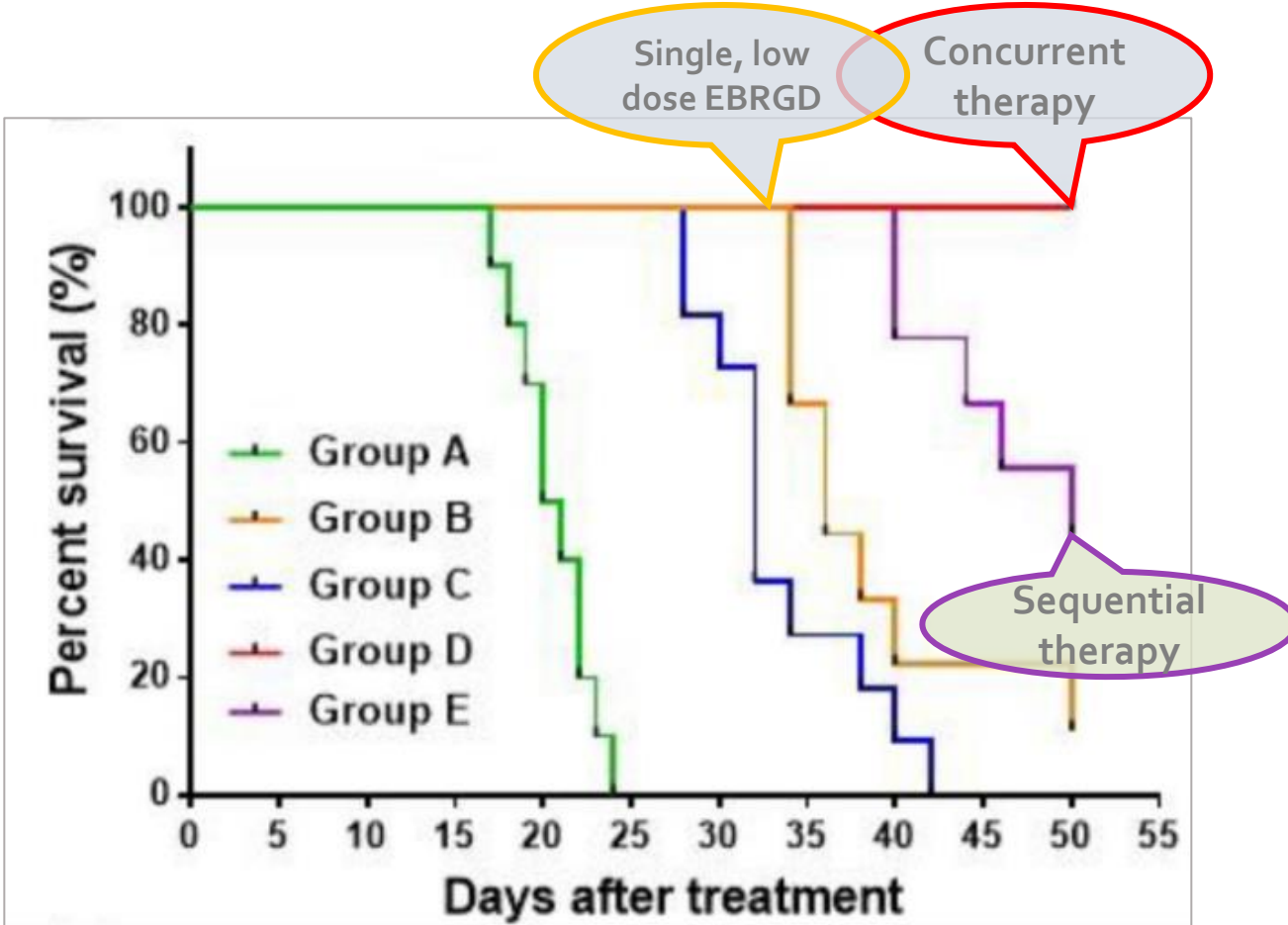
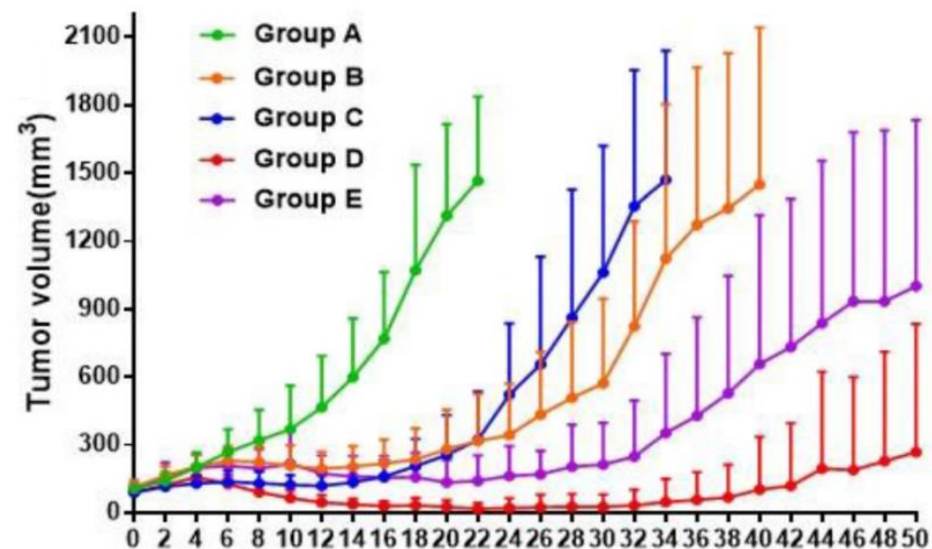
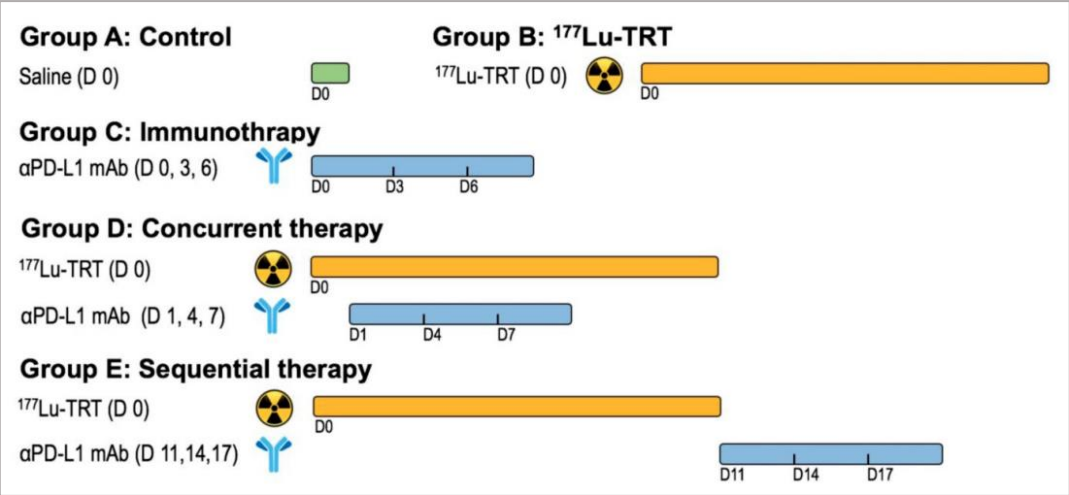
^{90}Y -EBRGD dose escalation: GBM tumor volume regression, improved survival and complete eradication of tumor at high dose in mice



Chen et al. J Nucl Med 2017; 58(4): 590-597



EBRGD enhances immunotherapy efficacy in colorectal cancer



Chen et al. Theranostics 2019; 9(25): 7948-7960

^{177}Lu -EBRGD/ anti-PD-L1 enhance anti-tumor efficacy

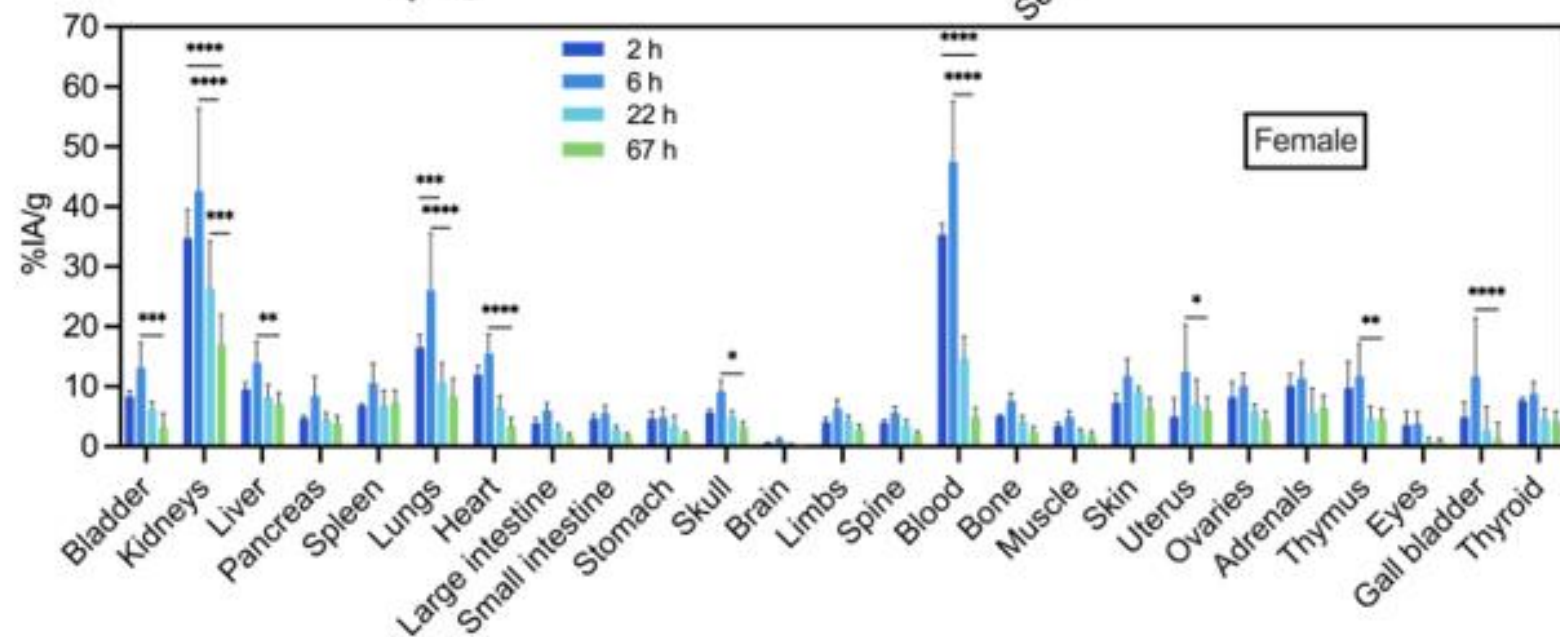
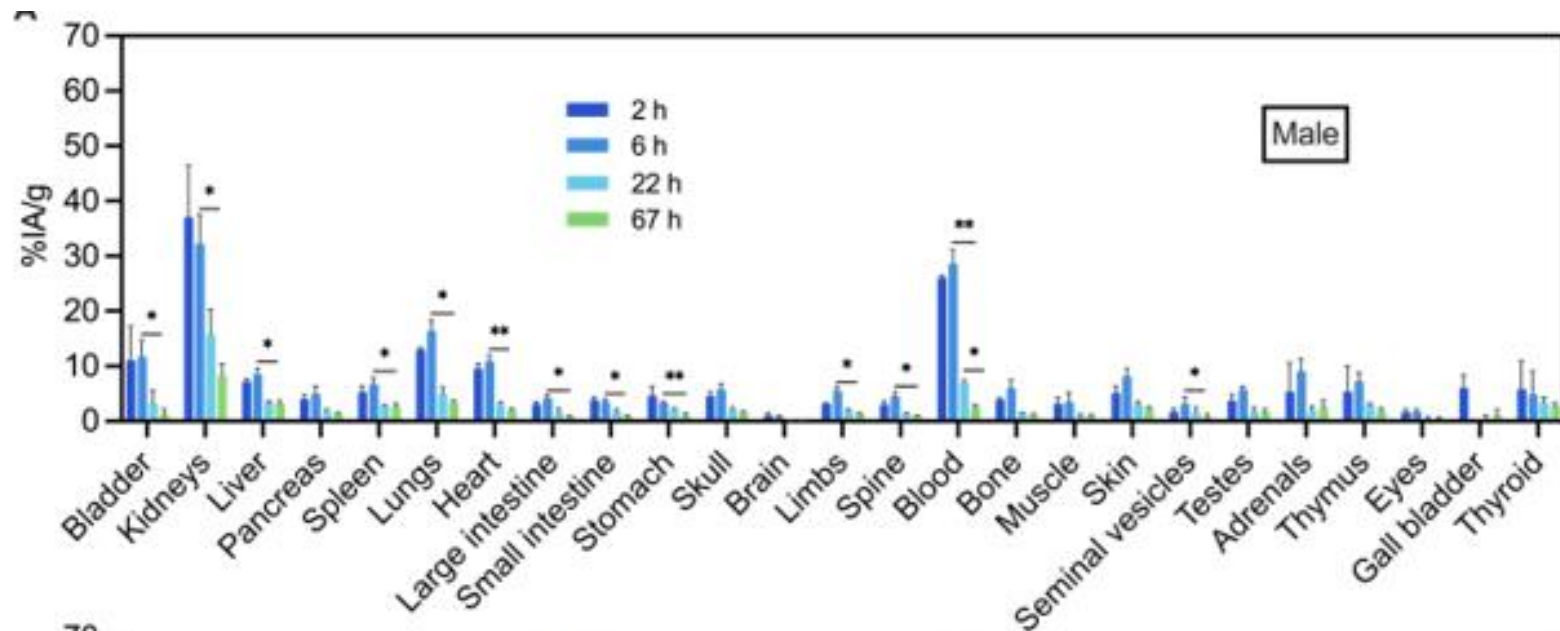
- This therapeutic combination may be a promising approach to treating metastatic tumors in which TRT can be used.
- Clinical translation of the result would suggest that concurrent rather than sequential blockade of the anti-PD-L1 combined with TRT improves overall survival and long-term tumor control.

Long acting [^{225}Ac]Ac-EBTATE is highly efficacious against somatostatin receptor-2-positive neuroendocrine tumors

- Fabrice N. Njotu¹, Humphrey Fonge^{1*} et. al.,.

Presented in 2024 SNMMI

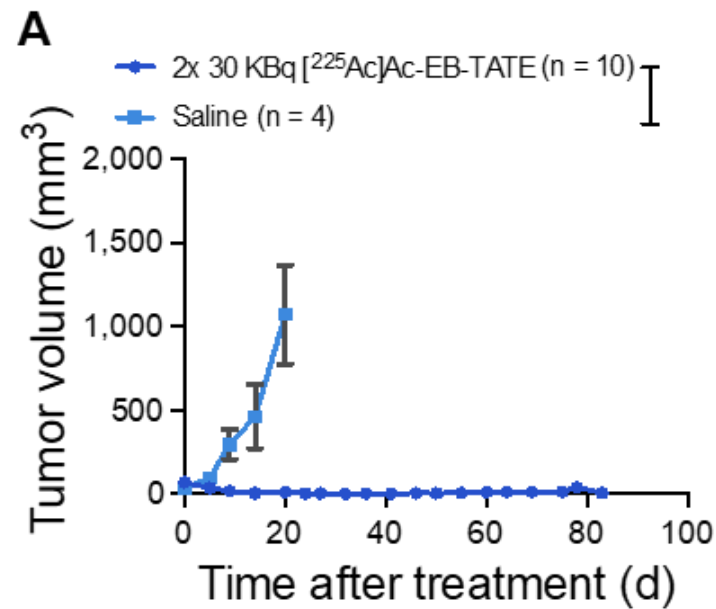
*University of Saskatchewan College of Medicine, Saskatoon, Saskatchewan;
and Molecular Targeting Technologies, Inc. West Chester, Pennsylvania



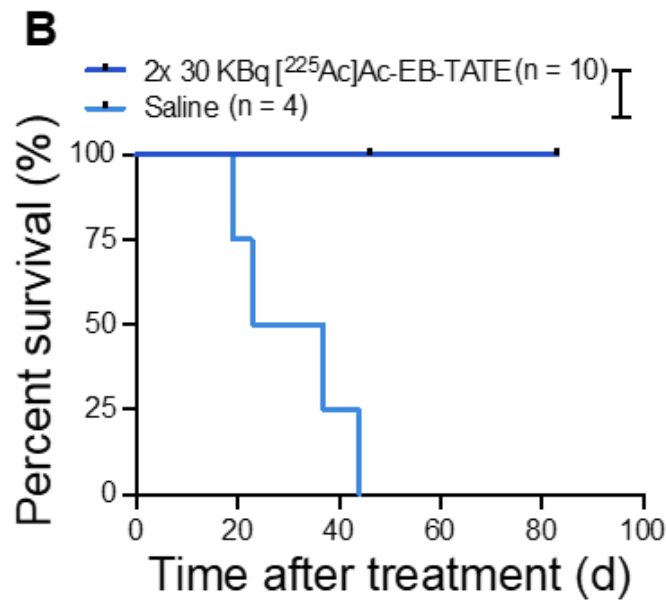
Biodistribution and pharmacokinetic of $[^{225}\text{Ac}]\text{Ac-EBTATE}$ in healthy BALB/c mice.

Therapy in NCH-H524 (SCLC).

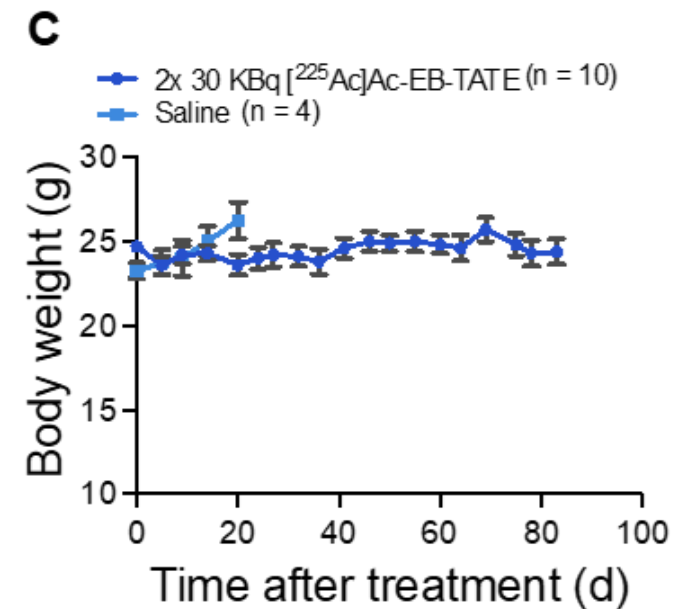
Average tumor growth



Kaplan Meier survival



Average body weights



²²⁵Ac-EBTATE IND-enablement update

- Completed GLP toxicology and GMP manufacturing
- Clinical protocols and sites identified for NET and SCLC
- Target IND submission 2025

Conclusions

- Two doses of ^{225}Ac -EBTATE at 34 kBq, 10 d apart, were well tolerated biochemically and hematologically for 28 d
- ^{225}Ac -EBTATE (2x 30 kBq, 10 d apart), in NCH-H524 showed 80% complete remission, 100% survival (d83) and 105.6% TGI, 2-fold more than ^{225}Ac -DOTATATE on d20
- ^{225}Ac -EBTATE (2x 30 kBq, 10 d apart) in NCH-H727 led to partial responses with 64.4% TGI on d28
- Using 60% less activity of ^{225}Ac -EBTATE is as effective as ^{225}Ac -DOTATATE