MTTI's Radiopharmaceuticals

A NEW GENERATION OF TARGETED RADIOTHERAPEUTICS (TRT)

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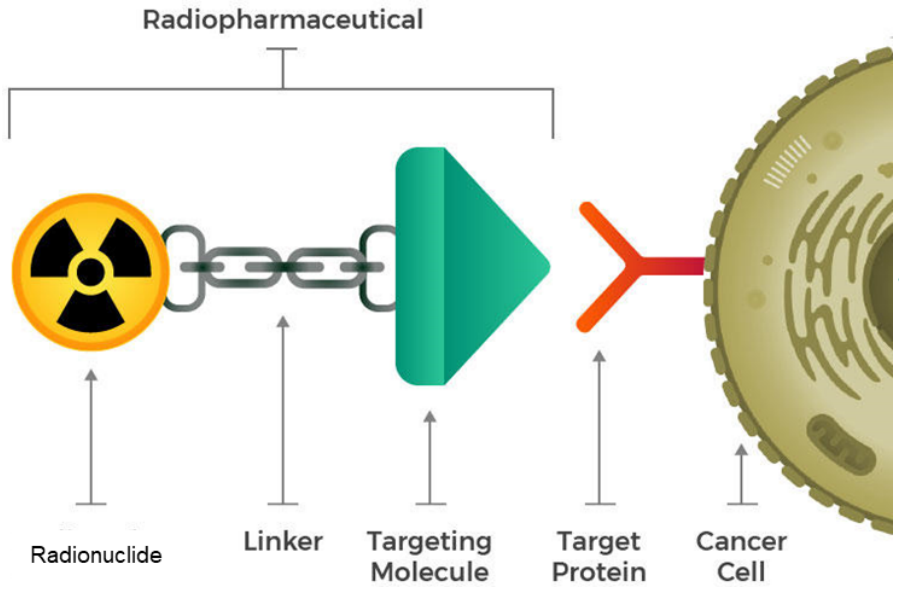
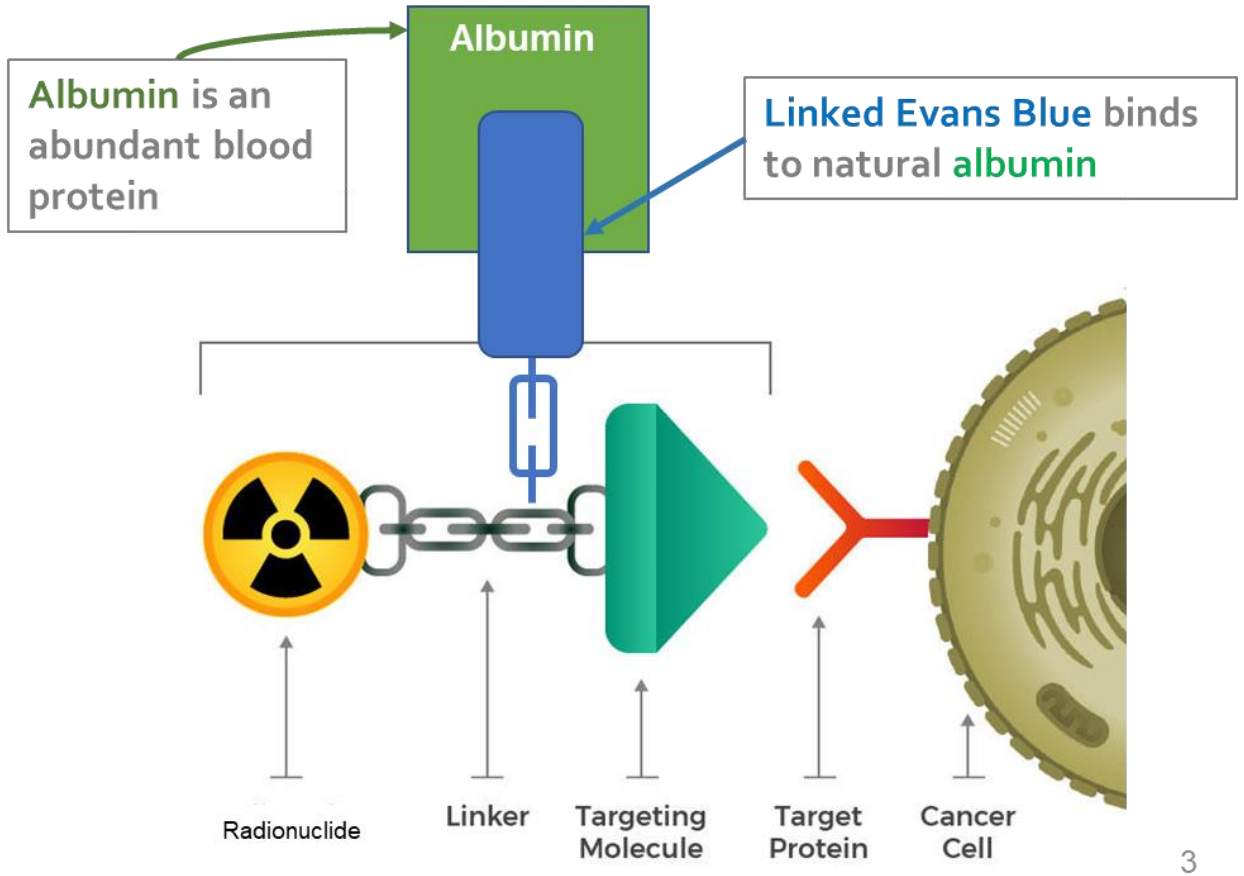
A long-acting, more effective TRT platform

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



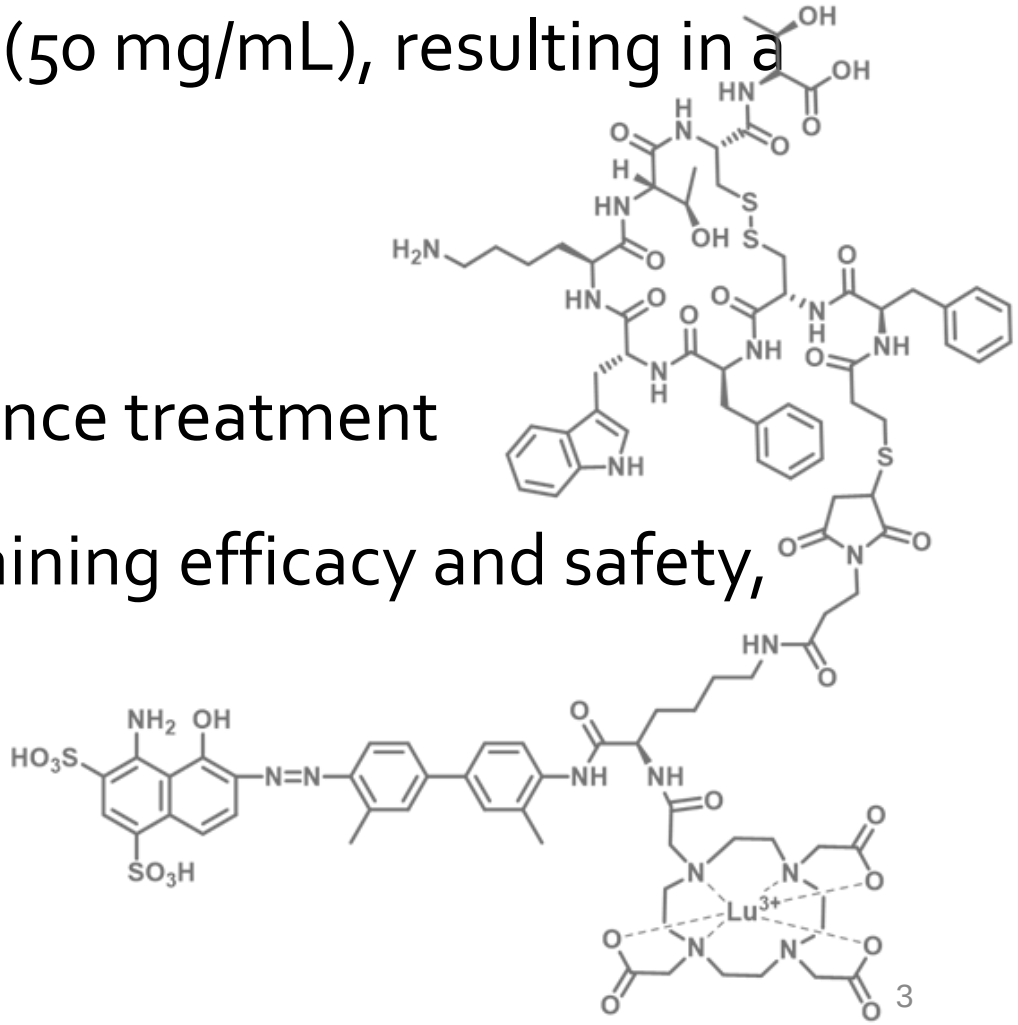
BREAKTHROUGH

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



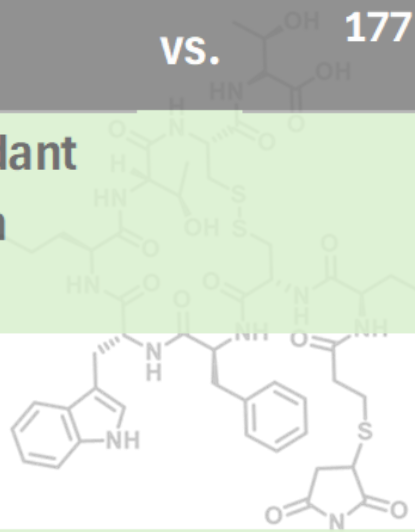
Transforming radiotherapy with an Evans blue (EB) moiety

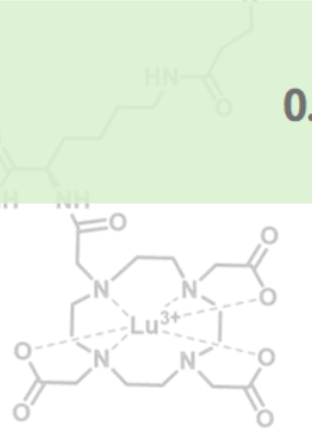
- EB binds to albumin, abundant in the blood (50 mg/mL), resulting in a longer circulatory half-life
- Each albumin binds 8-14 molecules of EB
- Better tissue absorption and retention enhance treatment
- Significantly lower isotope use while maintaining efficacy and safety, improves costs and health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

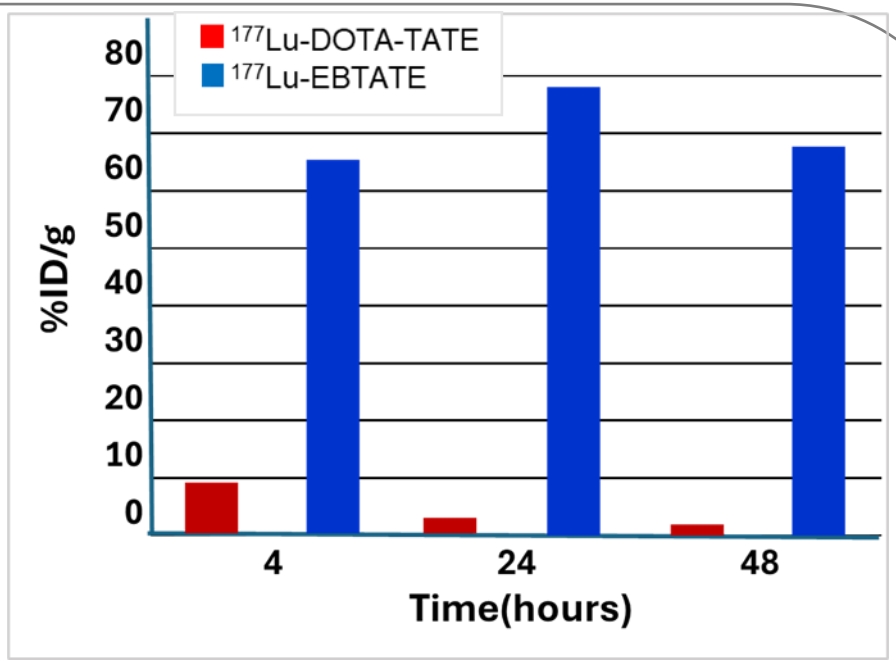


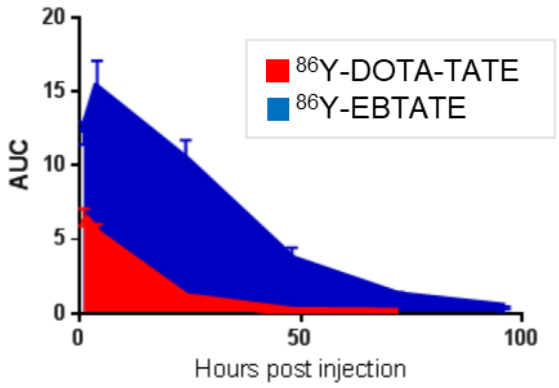


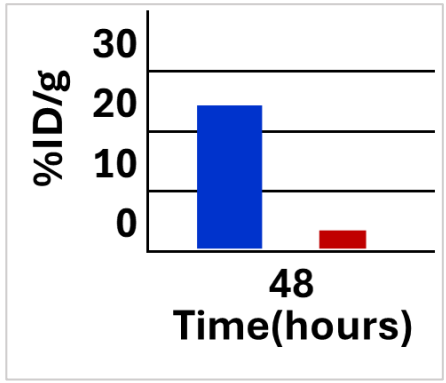
EB impact: Greater retention in HCT116 CRC tumor (Preclinical)

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

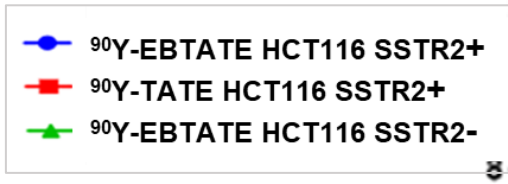
SSTR2+ tumor

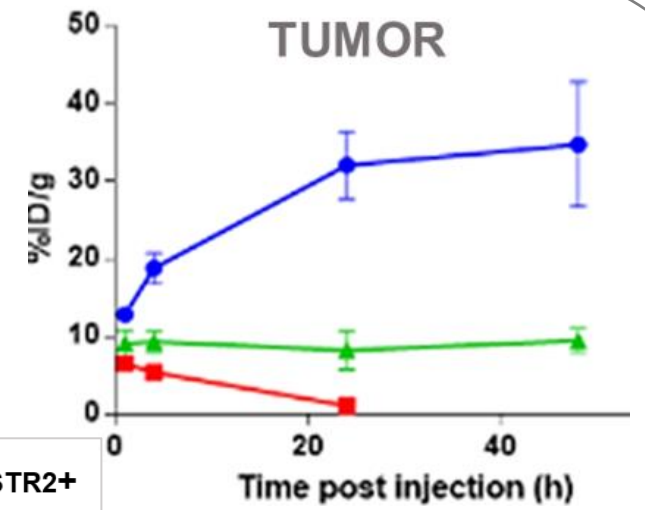


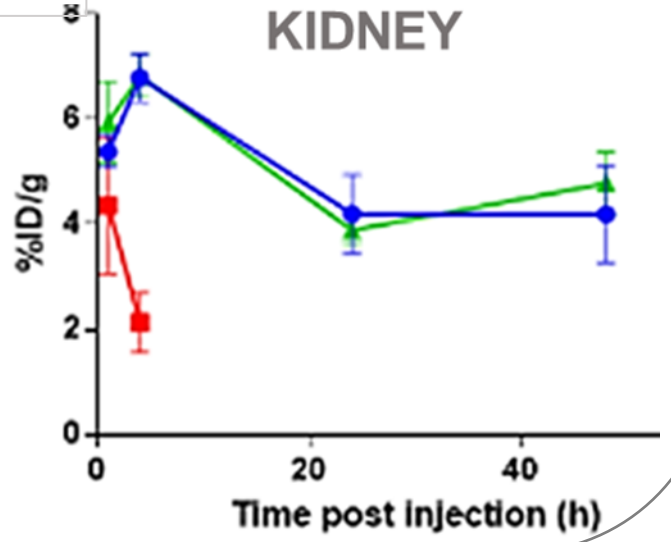




SSTR2 +/- tumor



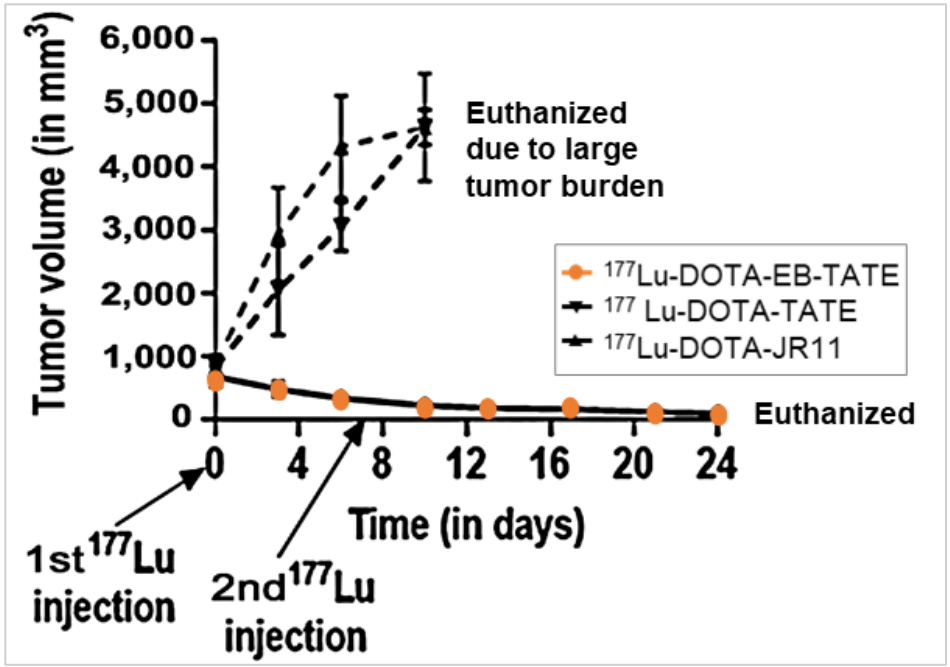


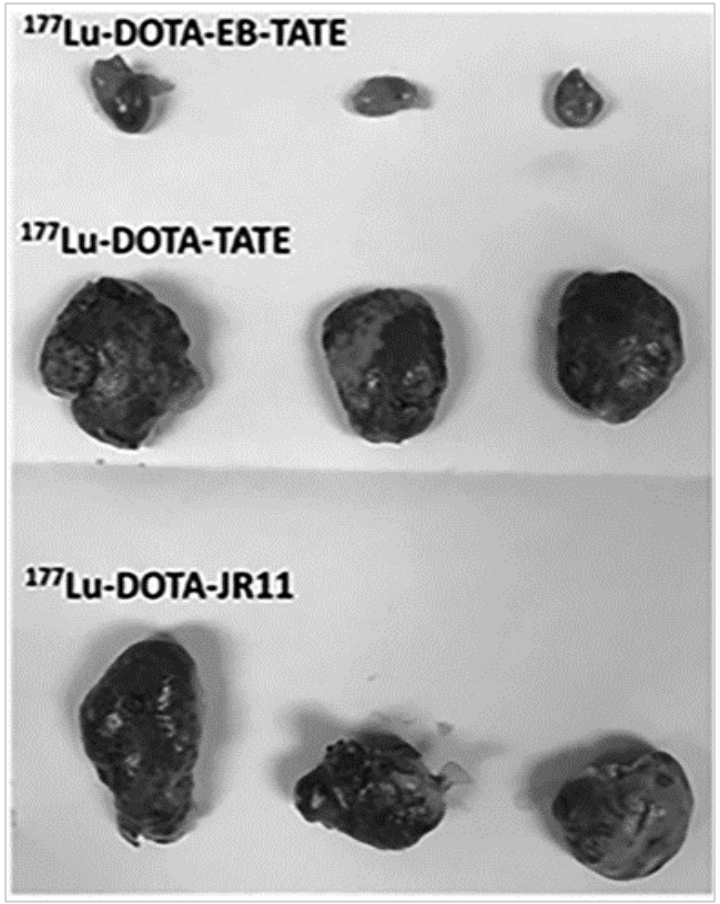


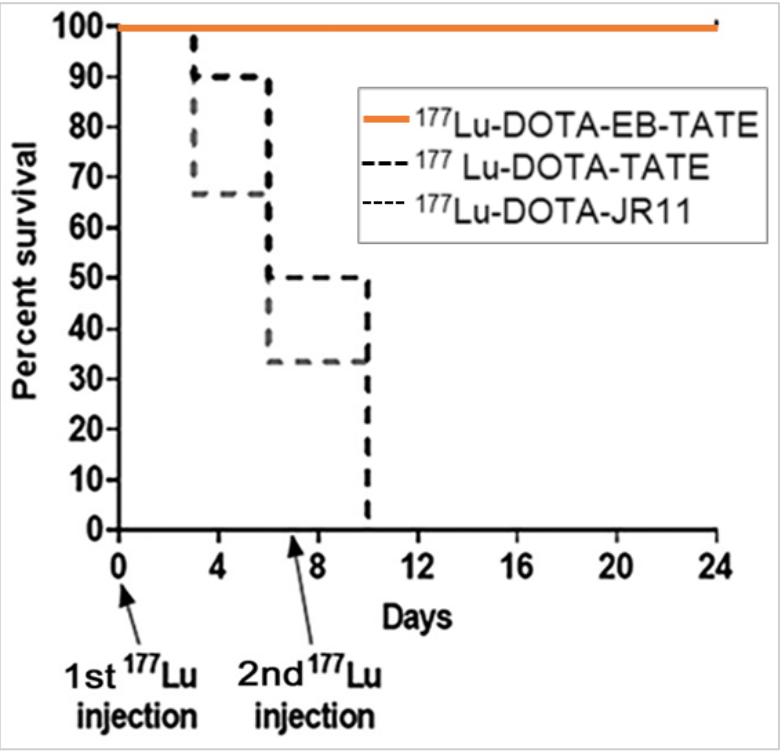
Theranostics 2018; 8: 734-745

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

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





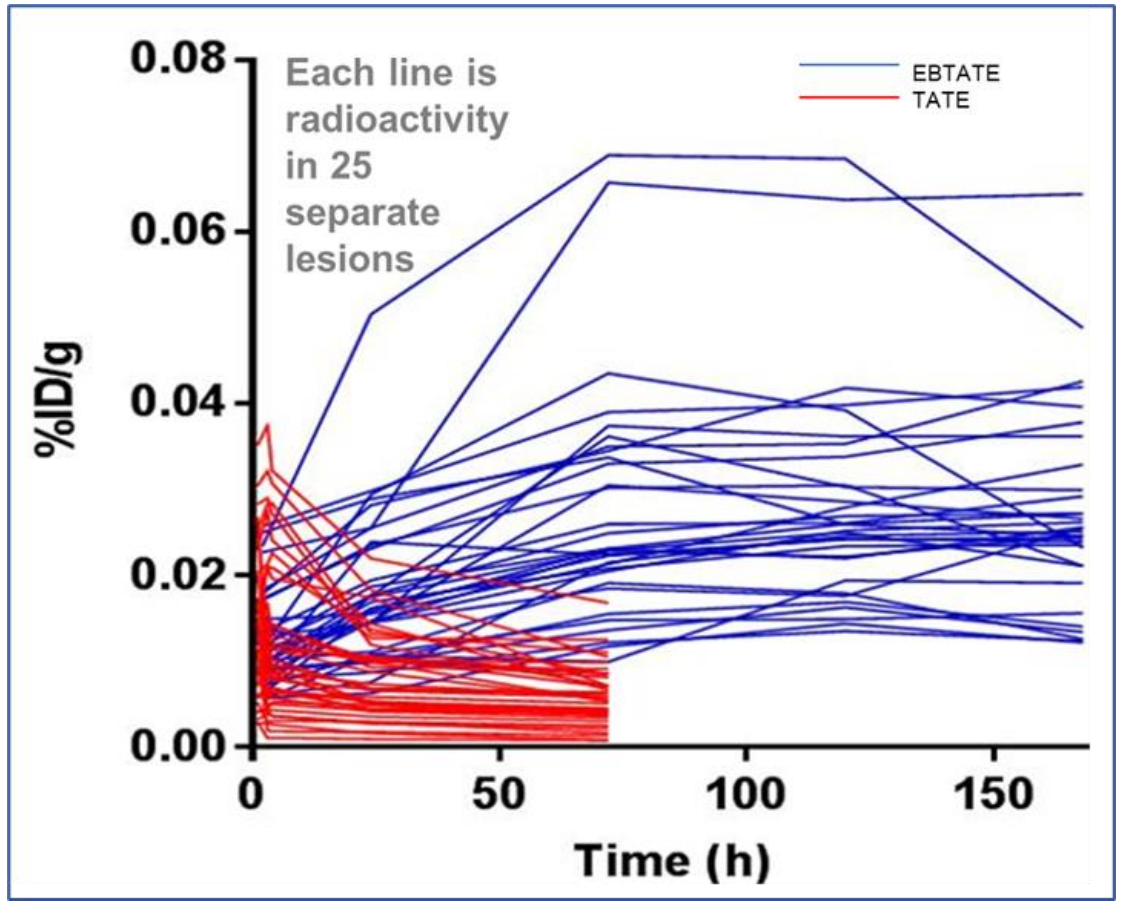


DOTA-EB-TATE is superior to other somatostatin analogues in the treatment of SSTR2-expressing tumors

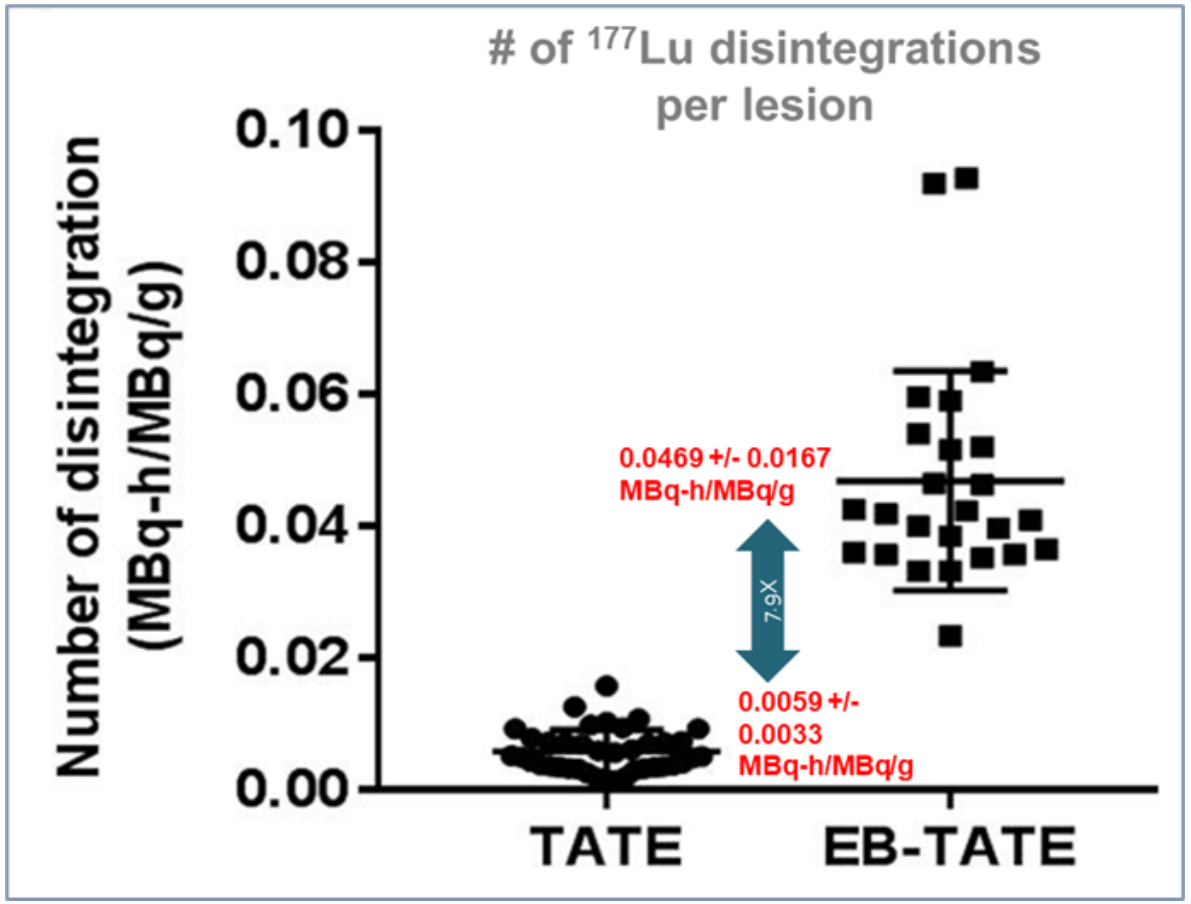
Clinical Cancer Res, 2021 Mar 1;27(5):1399-1409.

EB improves PK/PD in patients

EBTATE sustained tumor absorption in NET patients



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

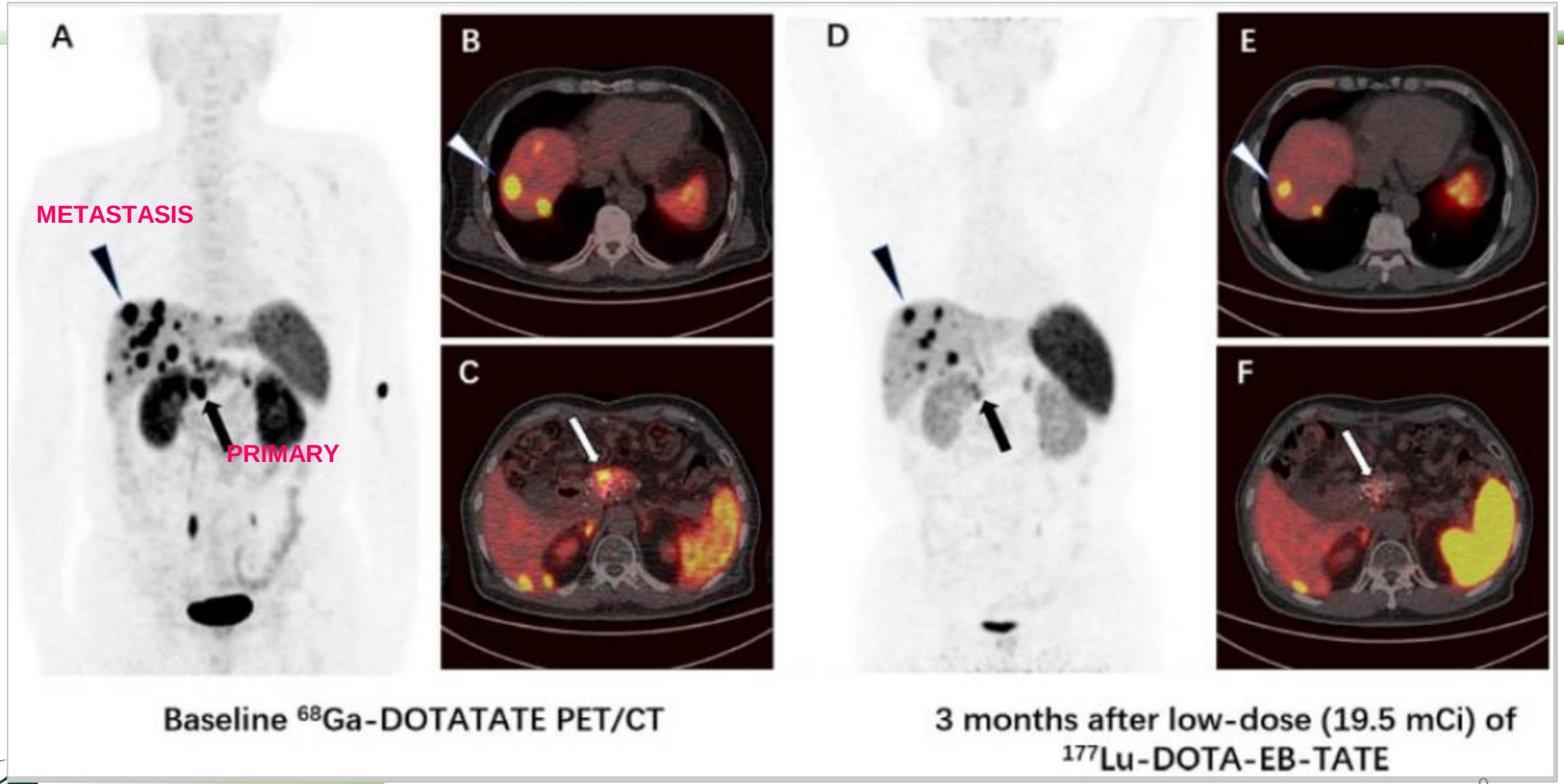


Zhang et al. J Nucl Med 2018; 59: 1699-1705

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	Preclincal 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			

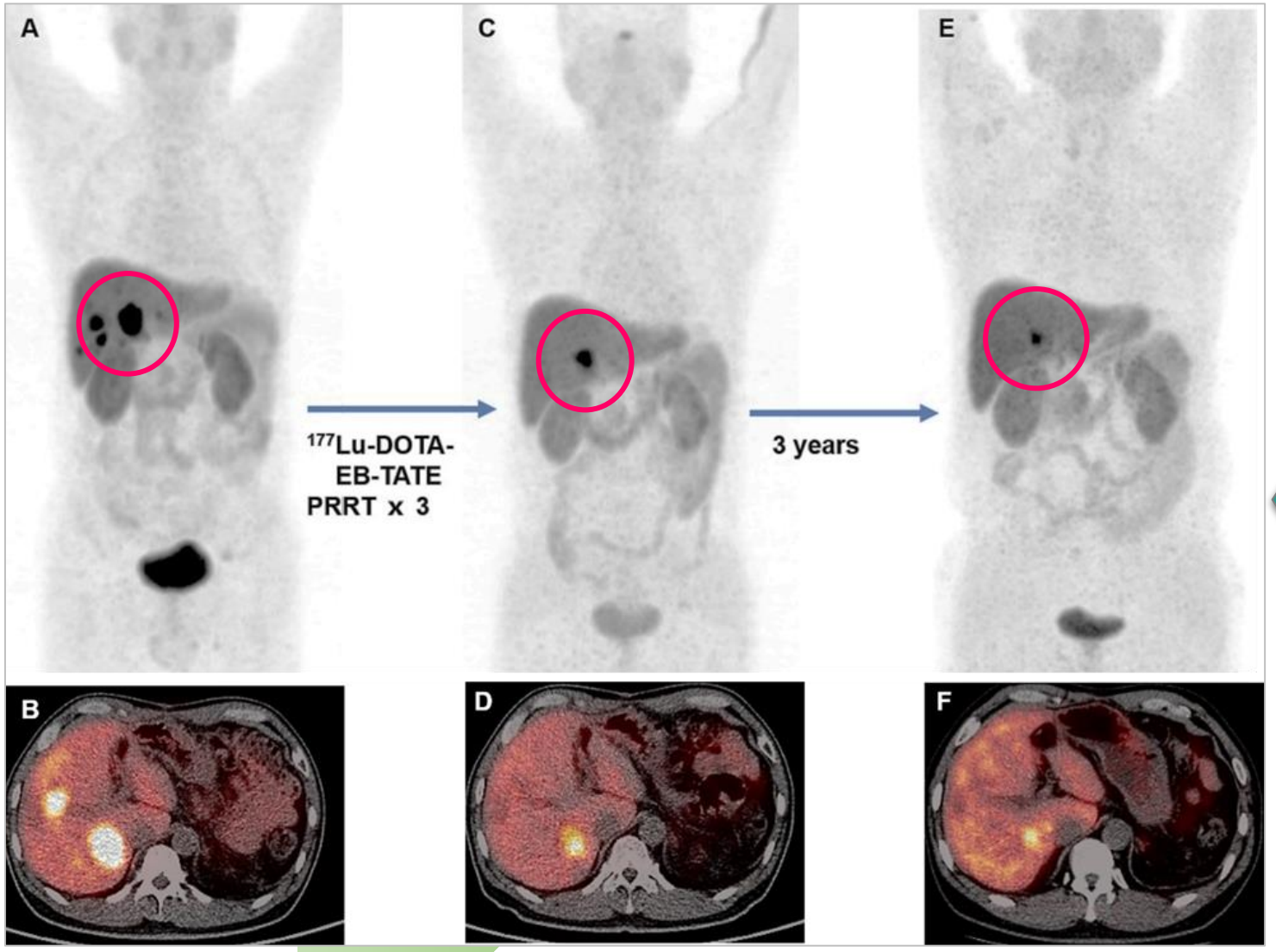
A single low dose (20 mCi) of EBTATE reduces NET tumor size



Wang et al. Theranostics 2018; 8(12): 3308-3316

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

2024 SNMMI Presentation; Fabrice N. Njotu, Humphrey Fonge *et. al.

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

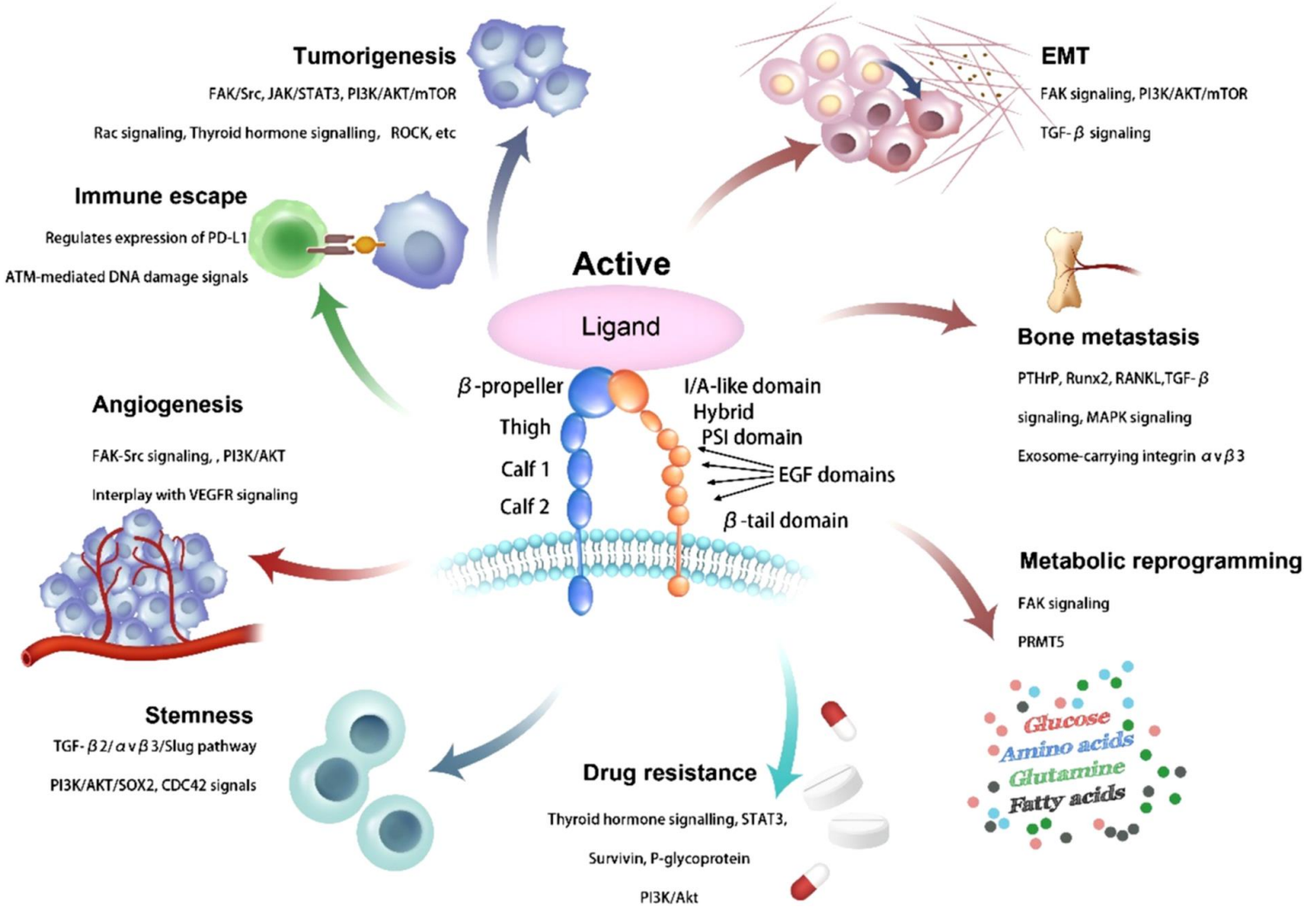
- Transforming radiotherapy with Evans blue(EB)
  - Greater ^{177}Lu-EBTATE uptake
  - Complete remission in AR42J pancreatic model
  - 8-fold greater retention in NET patients
  - Similar safety to ^{177}Lu-DOTATATE with 40% of the radioactivity
- ^{225}Ac-EBTATE showed 80% complete remission, 100%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

EBRGD

EBRGD targets αvβ3, an integrin with multiple roles in cancer

αvβ3 in every step of tumor progression:

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



Pharmacological Research 189 (2023) 106694

αvβ3 advantage as cancer target over other integrins

- **αvβ3 has low or no expression in normal tissues**
- **Expression level increases in tumors and correlates with tumor aggressiveness**
  - Some integrins, such as α2β1, decrease in tumor cells
- **αvβ3 interacts with growth factors highly expressed in tumors**
  - αvβ3 and FGFR interaction induces angiogenesis downstream of FGF binding, and αvβs and VEGFR2 promote VEGF-induced angiogenesis
- **αvβ3 is overexpressed in tumors with higher frequency than other integrins**

Tumour type	Integrins expressed*	Associated phenotypes
Melanoma	**αvβ3** and α5β1	Vertical growth phase [35,172–174] and lymph node metastasis[173,175]
Breast	α6β4 and **αvβ3**	Increased tumour size and grade[176], and decreased survival[177] (α6β4). Increased bone metastasis[36–38,64] (αvβ3)
Prostate	**αvβ3**	Increased bone metastasis[39]
Pancreatic	**αvβ3**	Lymph node metastasis[40]
Ovarian	α4β1 and αvβ3	Increased peritoneal metastasis[178] (α4β1) and tumour proliferation[179] (αvβ3)
Cervical	**αvβ3** and αvβ6	Decreased patient survival[41,180]
Glioblastoma	**αvβ3** and αvβ5	Both are expressed at the tumour–normal tissue margin and have a possible role in invasion[181]
Non-small-cell lung carcinoma	α5β1	Decreased survival in patients with lymph node-negative tumours[182]
Colon	αvβ6	Reduced patient survival[109]

* Not a complete list

Nat Rev Cancer. 2010 Jan; 10(1): 9–22.

αvβ3 integrin is overexpressed in >76% NSCLC patients*

- αvβ3 expressed in tumor and not in normal cells
- αvβ3 correlates with tumor grade, progression, metastases and advanced clinical stage

αvβ3 **overexpressed in many cancers**

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

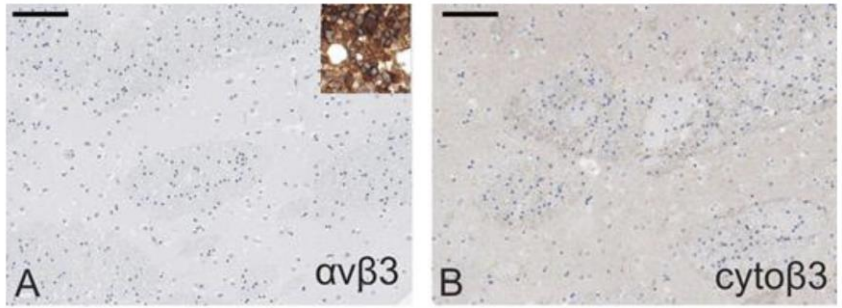
*Boger et al. Virchows Arch. 2014;464(1):69-78.; Echavidre et. al., Pharmaceutics. 2022;14(5):1053;
Jin et al. PLoS One. 2012;7(10):e48575, Kariya et. al. Comm Biol 2021;4:490.

αvβ3 overexpressed in neovascular cells & 60% of GBM patients*

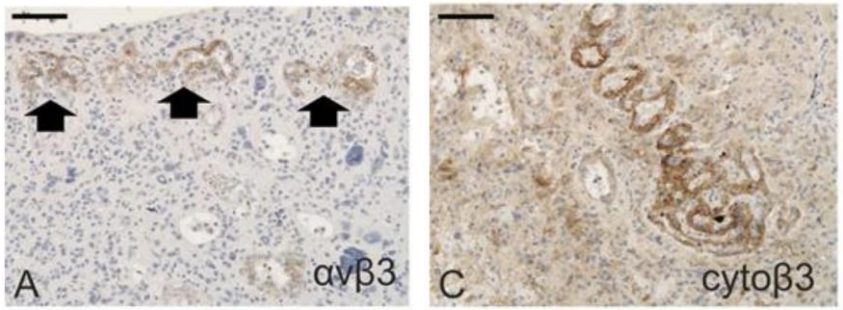
- αvβ3 integrin has – **low or no expression in normal tissues, overexpressed in many tumors**
- **RGD based PET tracer detects 100% primary lesions in cancer**
- αvβ3 was found in **neovascular** cells and **tumor cells**

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

αvβ3 has low/no expression in normal human brain samples



αvβ3 has elevated expression in GBM tumor vessels and parenchymal region



	αvβ3 positive tissues
Normal brain	0/78
Glioblastoma (WHO IV)	86/160

*Schittenhelm 2013, Echavidre 2022

Clinical development targeting αvβ3

Merck KGaA spent >10 years developing a targeted therapy for αvβ3 in GBM

- Cilengitide, a peptide αvβ3 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 αvβ3

Novartis began a Phase I trial with an αvβ3 and αvβ5 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)

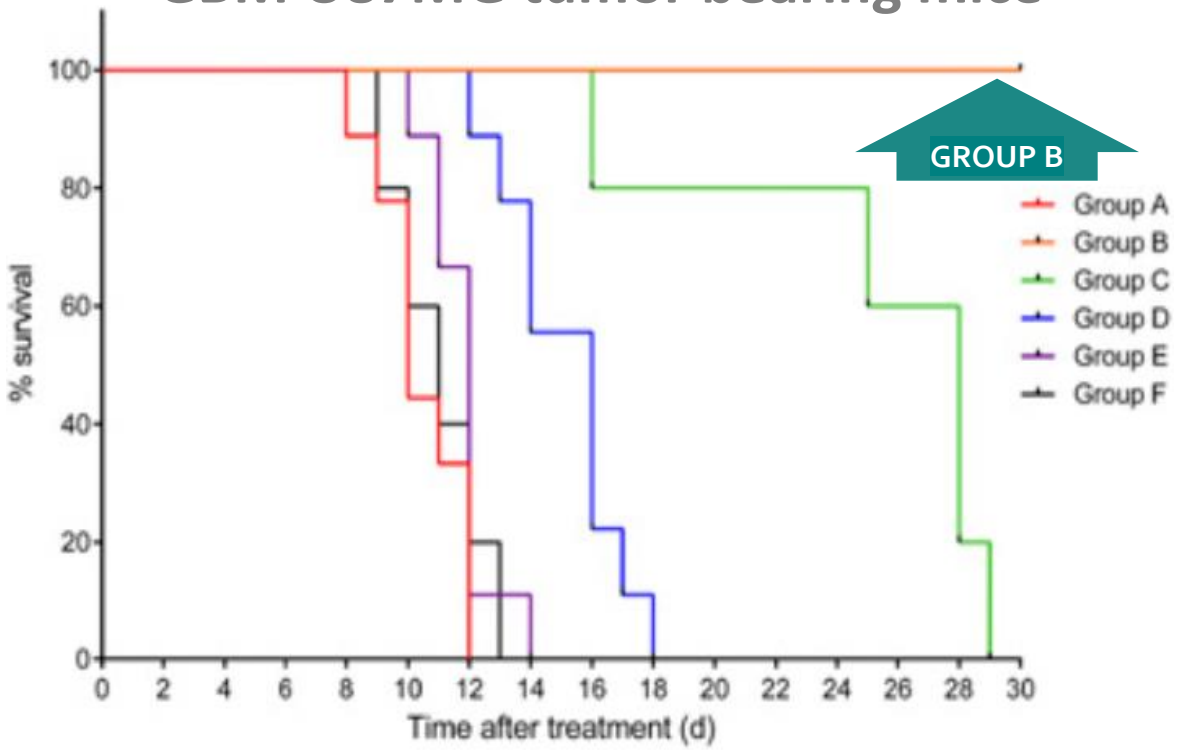
- FF58 is an αvβ3 and αvβ5 dual targeting molecule without the albumin binding motif

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)

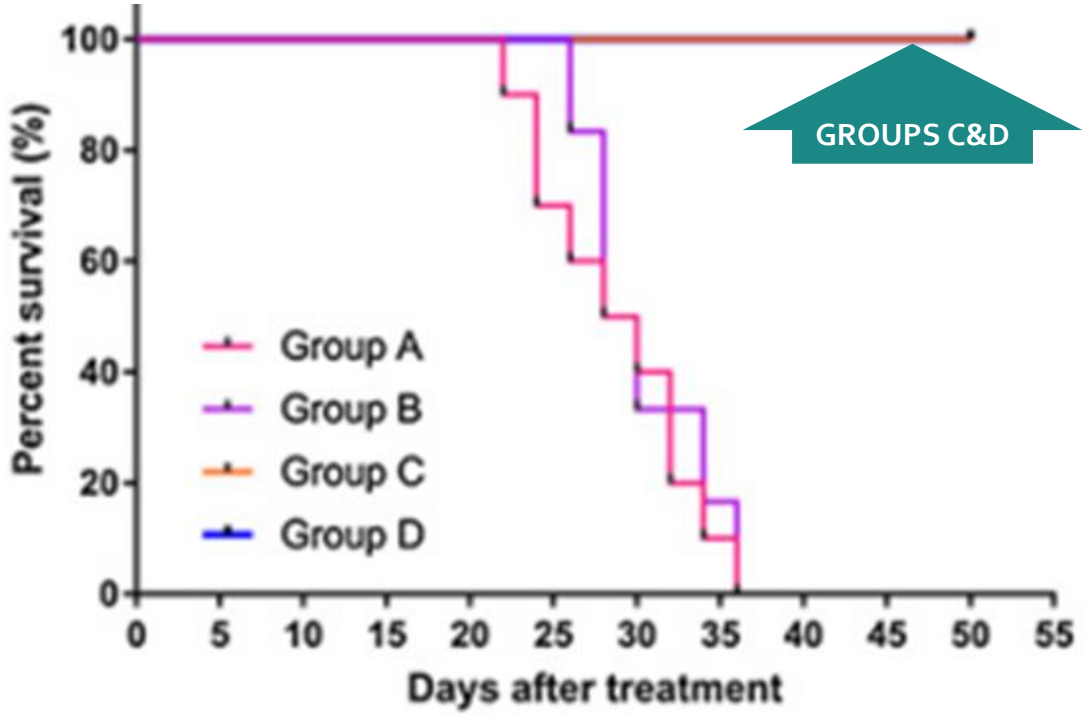
^{177}Lu & ^{90}Y EBRGD vs. RGD analogs

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 αvβ3 therapy failures

A validated target

- αvβ3 is required for angiogenesis and tumorigenesis in cancer
- αvβ3 therapy has been challenging

EBRGD advantage

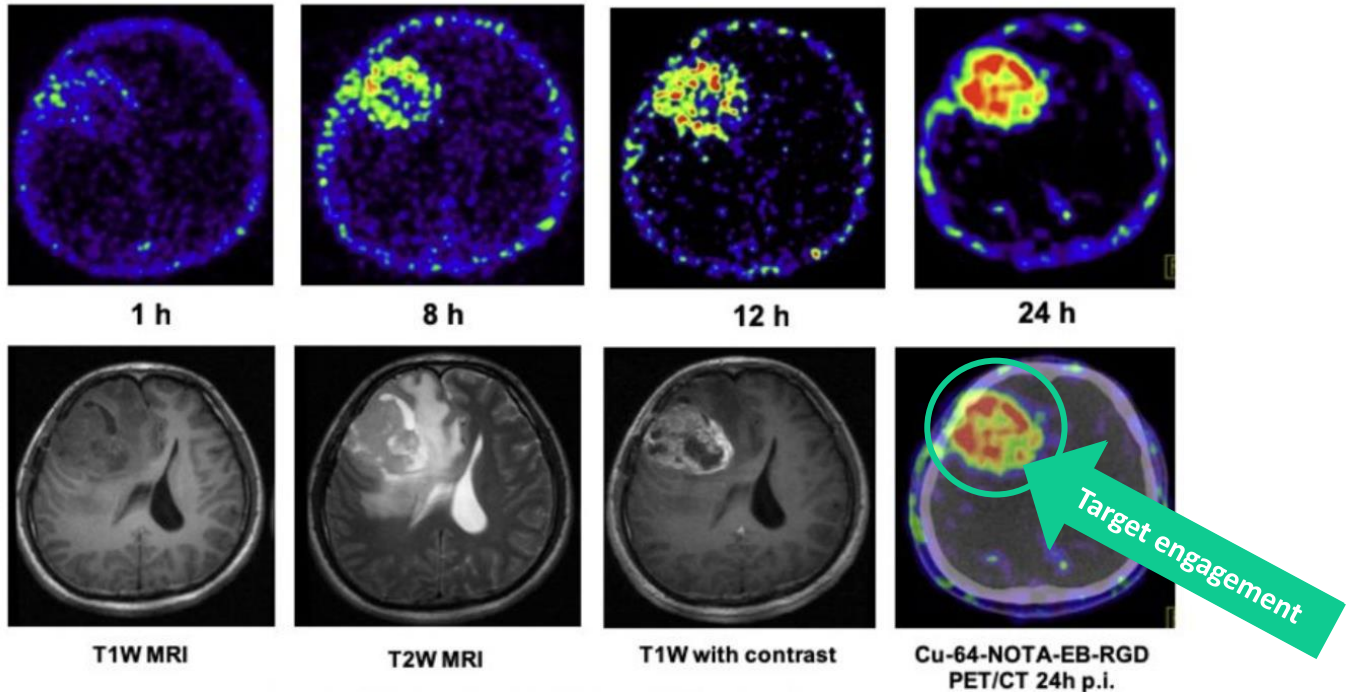
- EBRGD extends *in vivo* circulatory half-life and tumor residence time, enabling effective payload delivery

Strong *in vivo* efficacy

- Convincing efficacy in αvβ3 positive NSCLC, CRC and GBM model

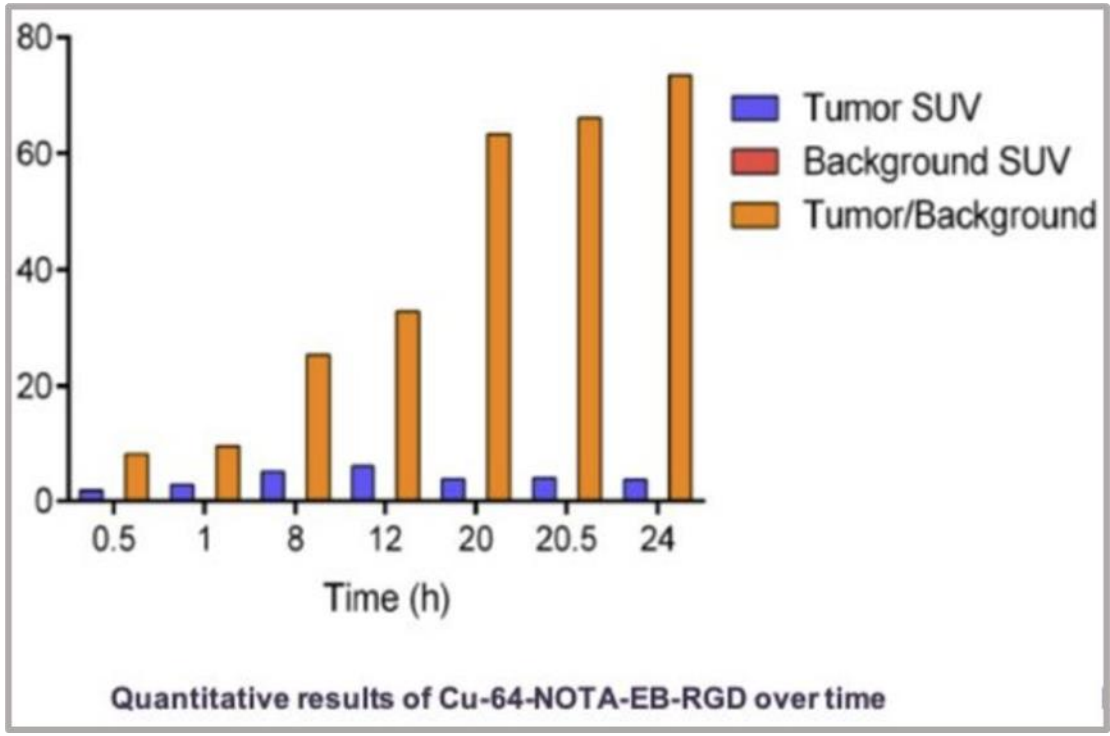
^{64}Cu-EBRGD – robust target engagement in GBM patients

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

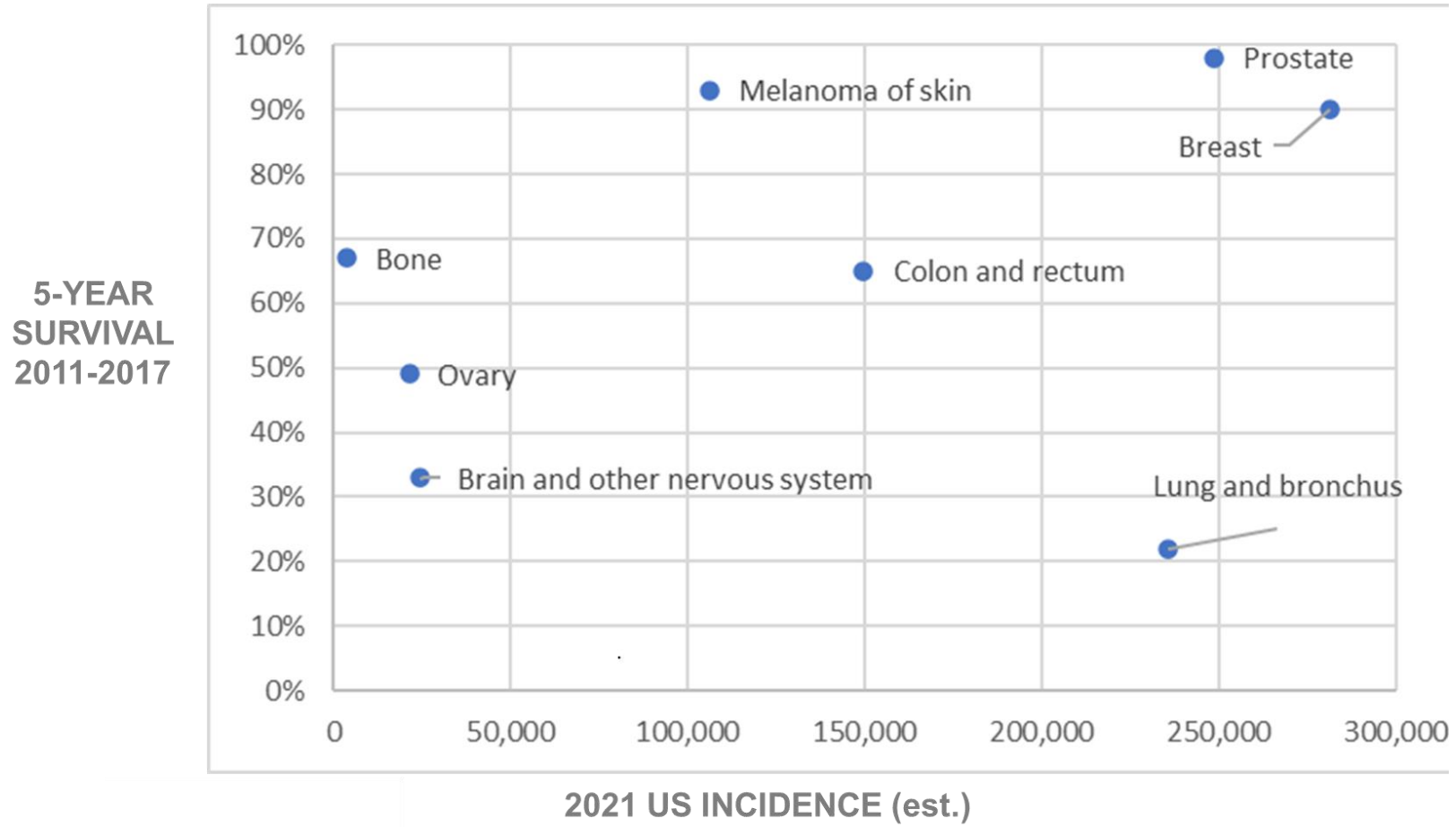


Zhang et al. J Nucl Med 2020; 61(Suppl 1): 349

EBRGD Opportunities

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

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



Summary

- αvβ3 is overexpressed in NSCLC, CRC, GBM and many other cancers
- EBRGD demonstrated:
  - ✓ efficacy in NSCLC, CRC and GBM models
  - ✓ tumor eradication in high expressing PDXαvβ3+
  - ✓ 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				

M · T · T · I

MTTI Team

Deep industry experience and record of drug approval

Chris Pak, PhD
- President & CEO

centocor · Mallinckrodt · Scotgen Biopharmaceuticals

Jeffrey Mattis, PhD,
- SVP Regulatory Affairs

centocor · Formula Pharmaceuticals

Bryan Gray, PhD,
- SVP Product Development

SB SmithKline Beecham · ZYNAXIS · PTI RESEARCH

Jianwei Xu, PhD
- CBO

McKinsey & Company · Cambridge Solutions Pharmaceutical Consulting

John Farah, PhD
- Executive Advisor

Cephalon · MELIOR DISCOVERY · AEOLUS PHARMACEUTICALS

Michael Silvon PhD, MBA
- SVP Business Development

CHARLES RIVER LABORATORIES · BASi · ZENECA

Clinical team/advisors

Jerry Huang, MD PhD - SVP Clinical Development

NOVARTIS · TAIHO ONCOLOGY, INC. · BeiGene

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

Penn Medicine

Chief, Division of Nuclear Medicine & Clinical Molecular Imaging

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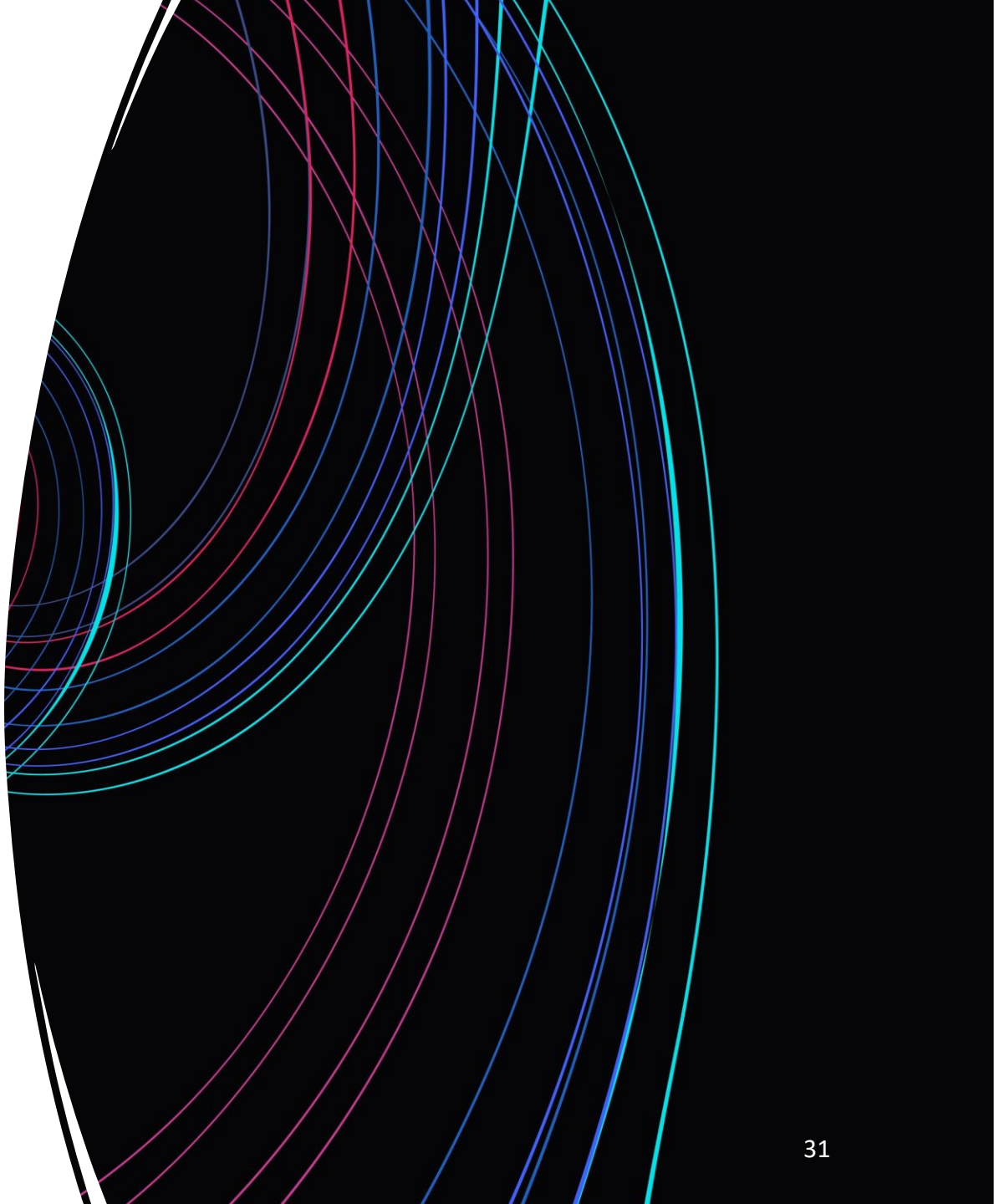
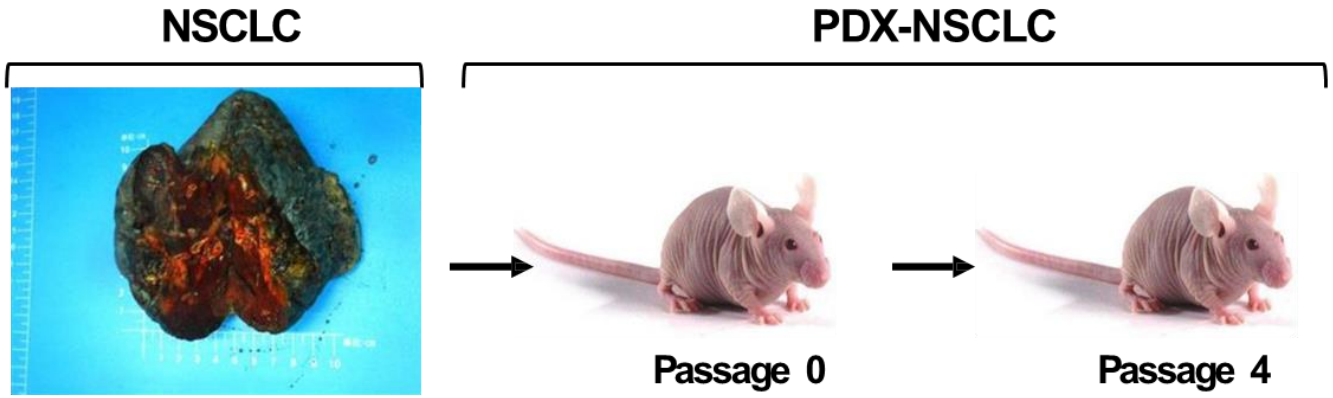
Appendices:

Preclinical studies

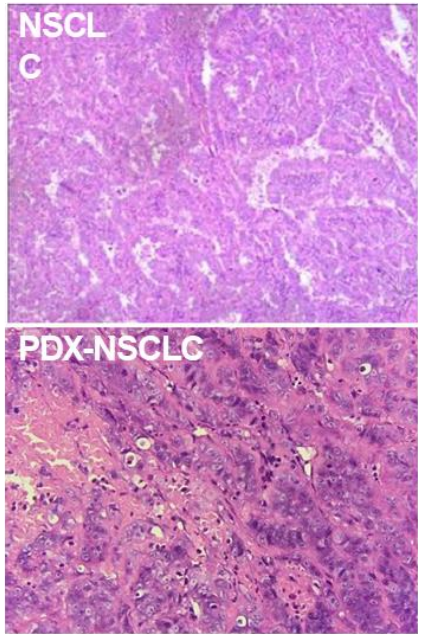
- ^{177}Lu-EBRGD
  - NSCLC (PDX)
  - GBM (U87MG)
  - CRC (MC38)
- ^{225}Ac-EBTATE

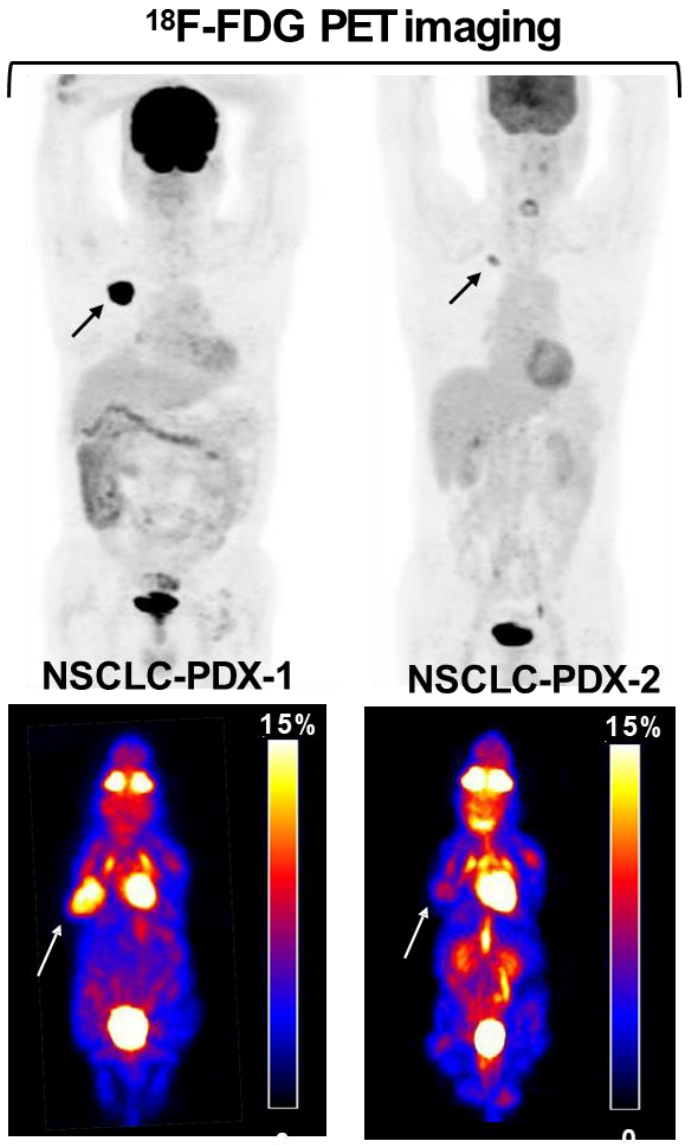


Establishment of patient-derived xenografts in NSCLC (PDX-NSCLC)

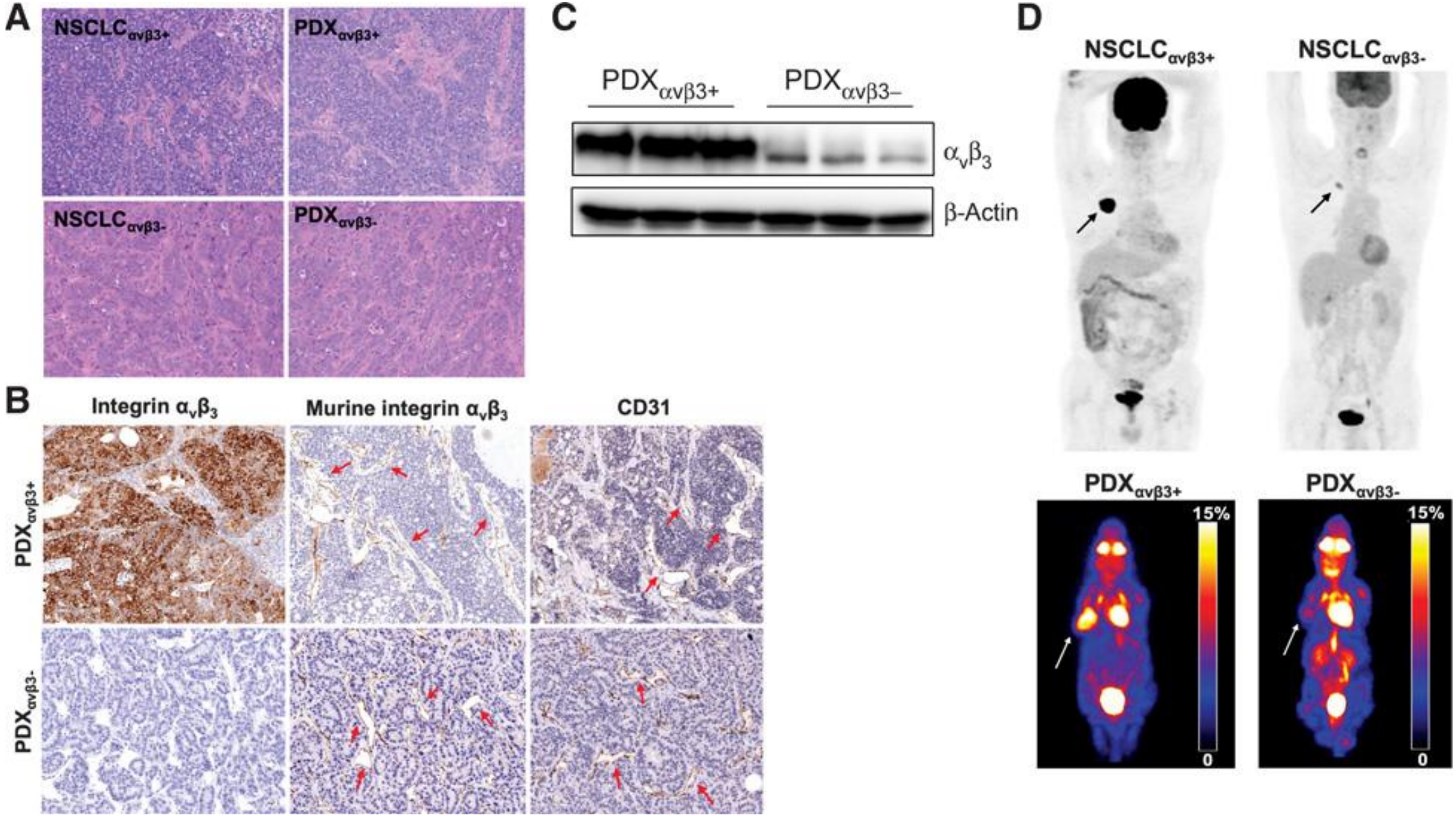


IHC	NSCLC	PDX-NSCLC
CK7	+	+
TTF-1	+	+
Napsin-A	+	+
P63	+	+
SY	–	–
CK5/6	–	–
Ki-67%	70%	70%

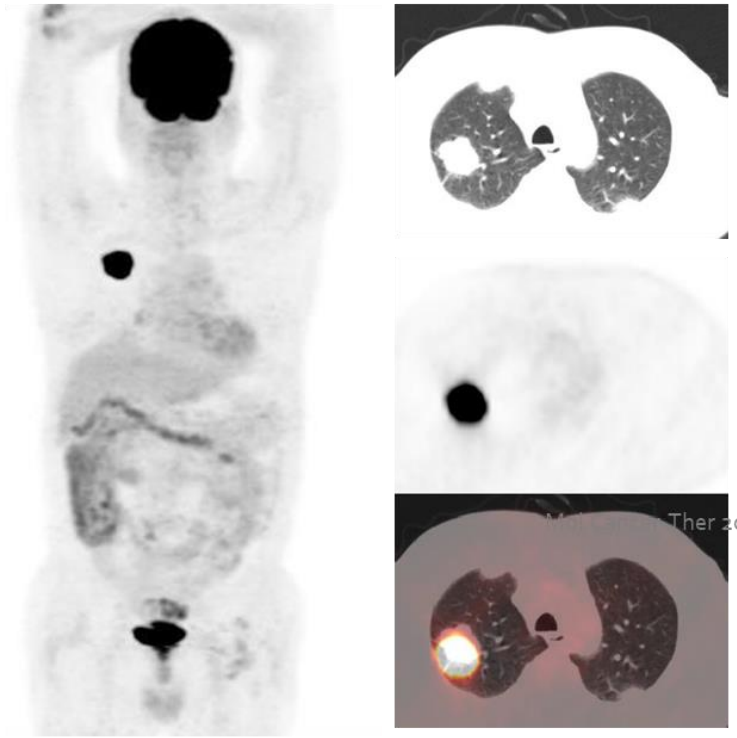




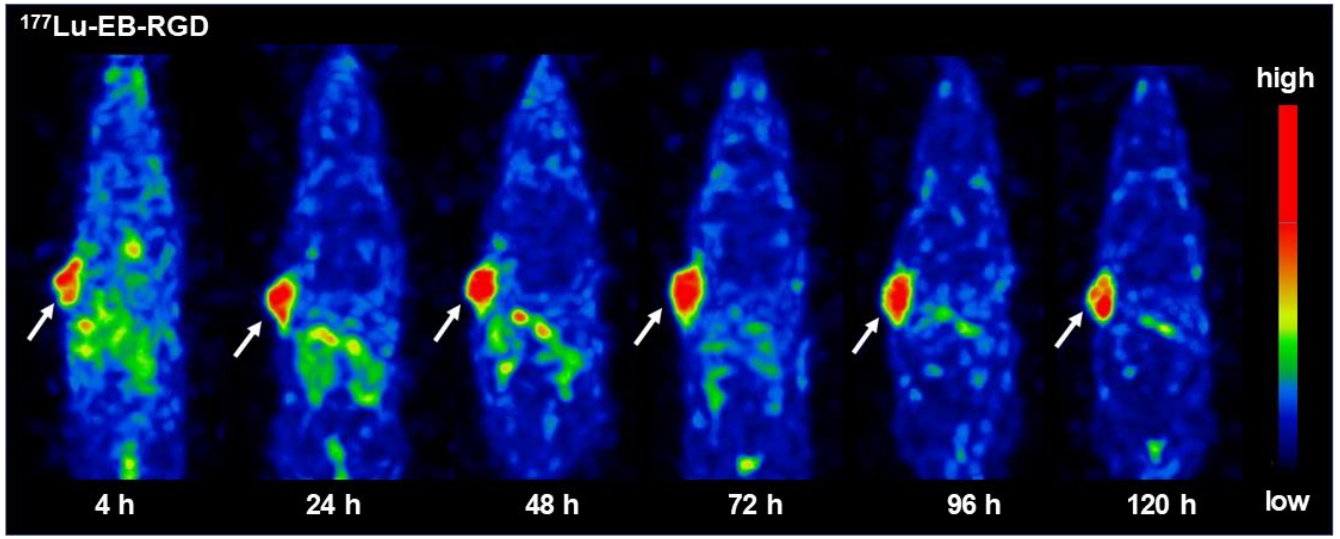
Mol Cancer Ther 2020;19:2034–43


A
NSCLC$_{\alpha v\beta 3+}$
PDX$_{\alpha v\beta 3+}$
NSCLC$_{\alpha v\beta 3-}$
PDX$_{\alpha v\beta 3-}$
B
Integrin $\alpha_v\beta_3$
Murine integrin $\alpha_v\beta_3$
CD31
PDX$_{\alpha v\beta 3+}$
PDX$_{\alpha v\beta 3-}$
C
PDX$_{\alpha v\beta 3+}$
PDX$_{\alpha v\beta 3-}$
$\alpha_v\beta_3$
β-Actin
D
NSCLC$_{\alpha v\beta 3+}$
NSCLC$_{\alpha v\beta 3-}$
PDX$_{\alpha v\beta 3+}$
PDX$_{\alpha v\beta 3-}$
15%
0
15%
0

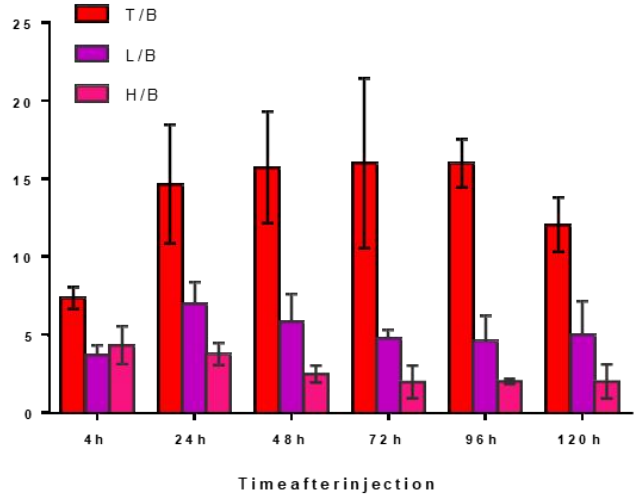
^{177}Lu-EB-RGD SPECT imaging in $\alpha_v\beta_3$-positive PDX-NSCLC

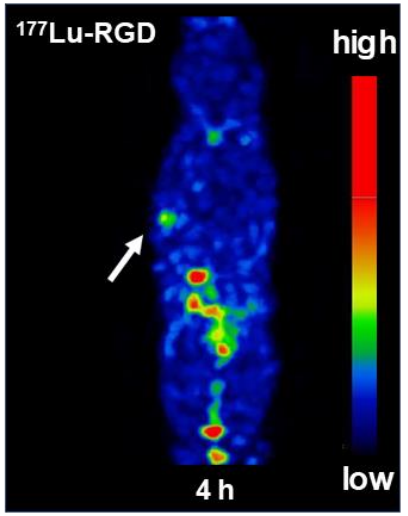


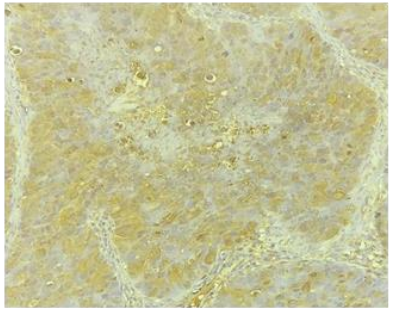
FDG PET imaging in the patient with lung adenocarcinoma, $\alpha_v\beta_3$ high expression



Mol Cancer Ther 2020;19:2034–43







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

Mol Cancer Ther 2020;19:2034–43

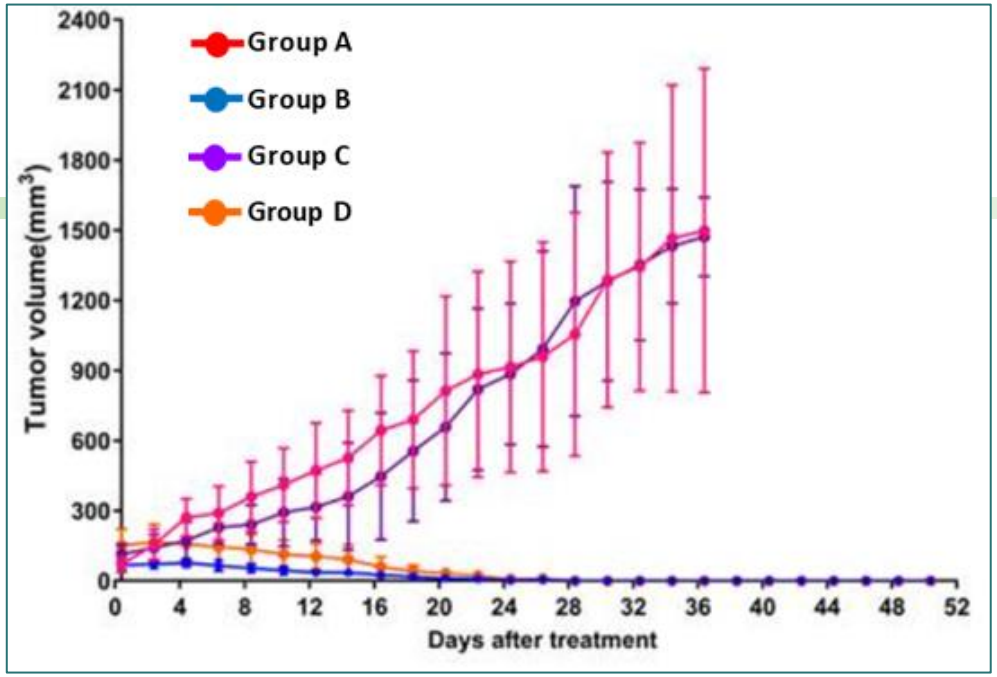
^{177}Lu-EBRGD resulted in tumor volume regression and improved survival of αvβ3+ PDX (NSCLC) mice

Day 0 Group A: Saline

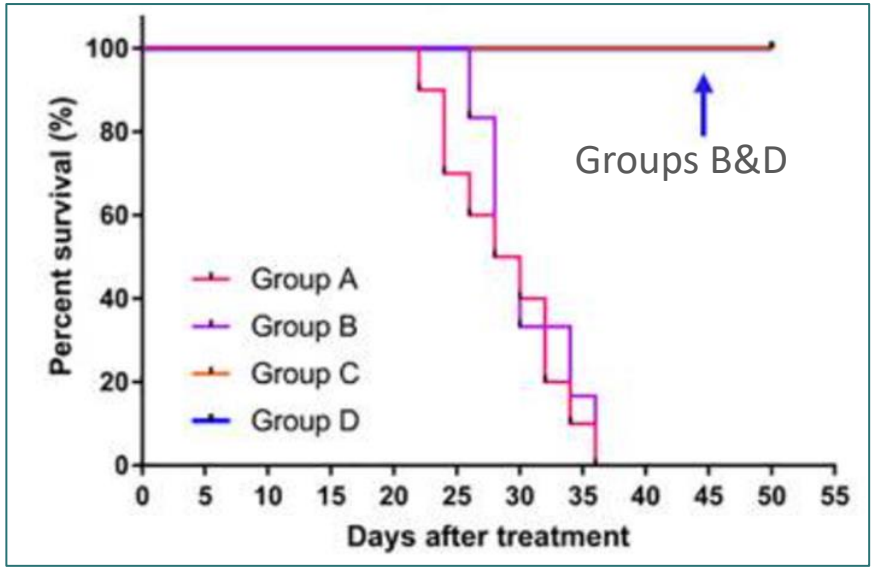
Day 0 Group B: ^{177}Lu-EB-RGD (18.5 MBq)

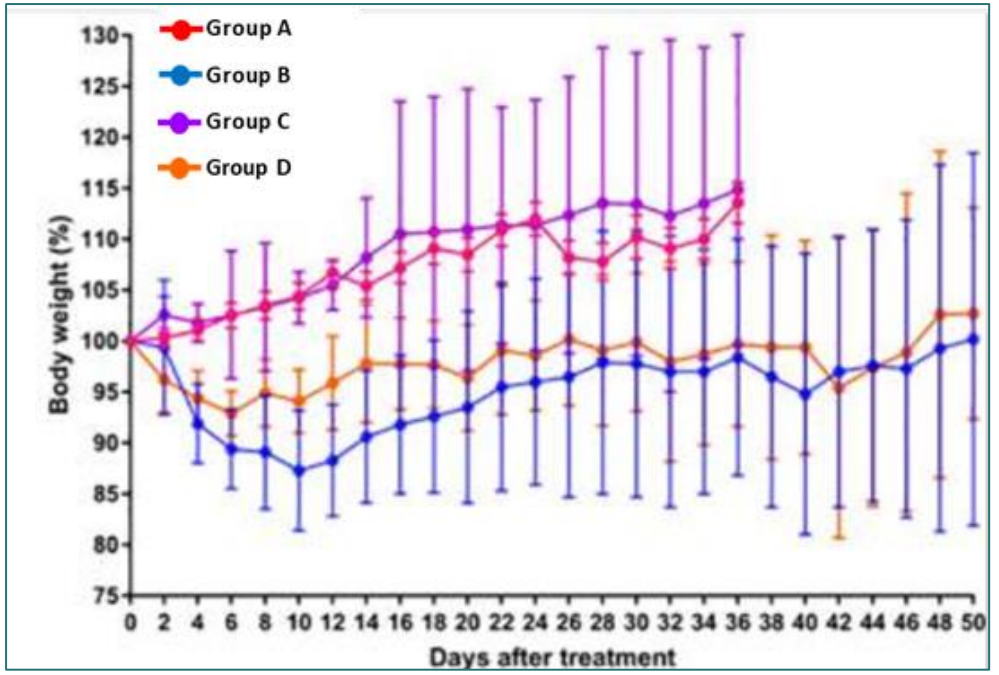
Day 0 Group C: ^{177}Lu-RGD (29.6 MBq)

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

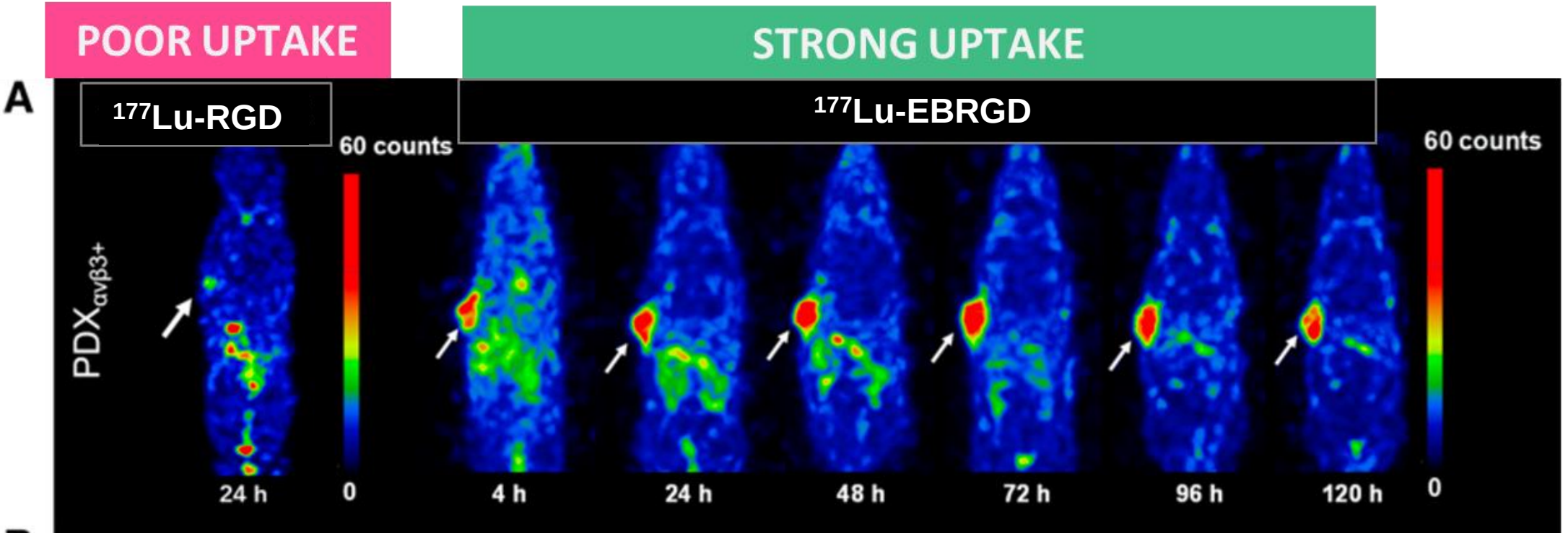




Zhao et al. Mol Cancer Ther 2020; 19(10): 2034-2043

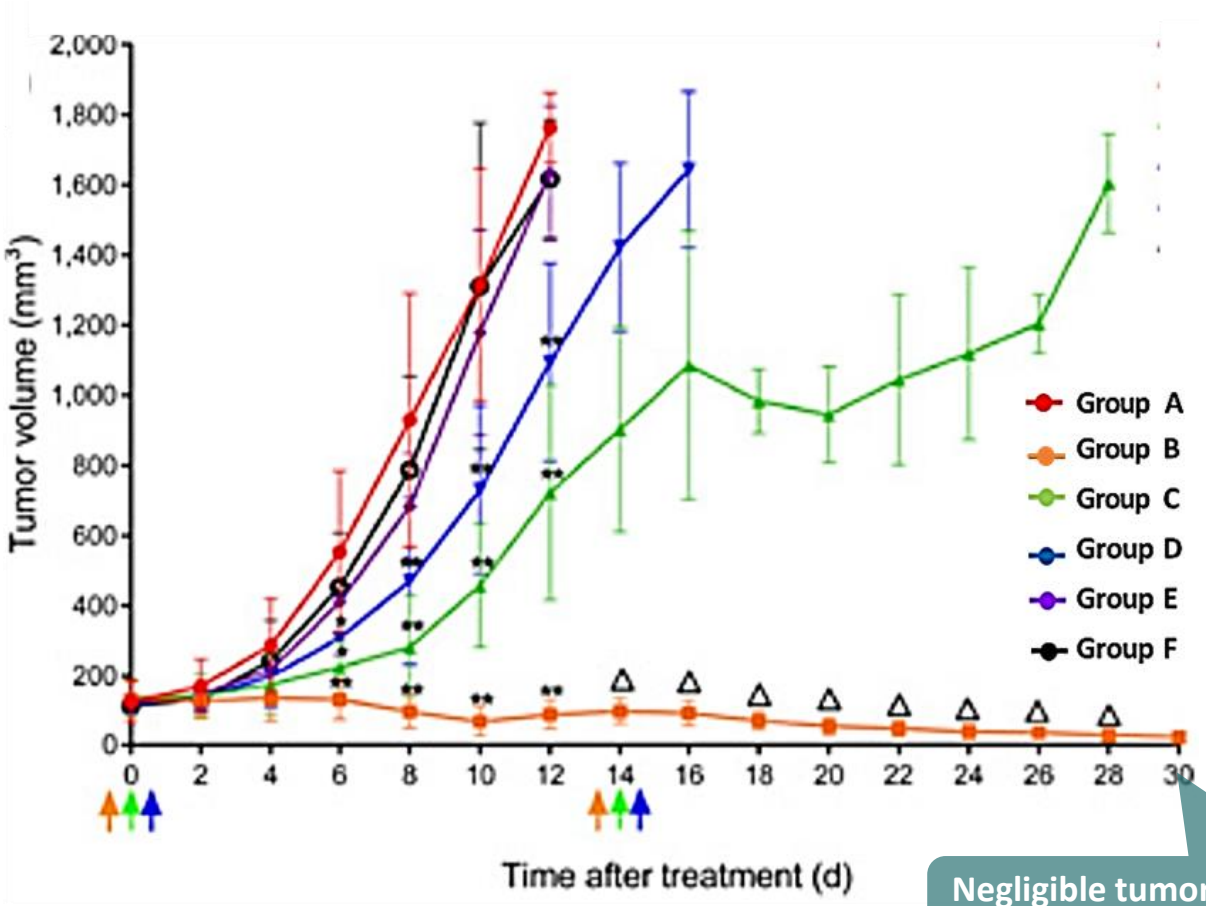
^{177}Lu-EBRGD vs ^{177}Lu-RGD SPECT imaging in $\alpha_v\beta_3$ positive PDX-NSCLC

EBRGD's longer residence time significantly improves uptake

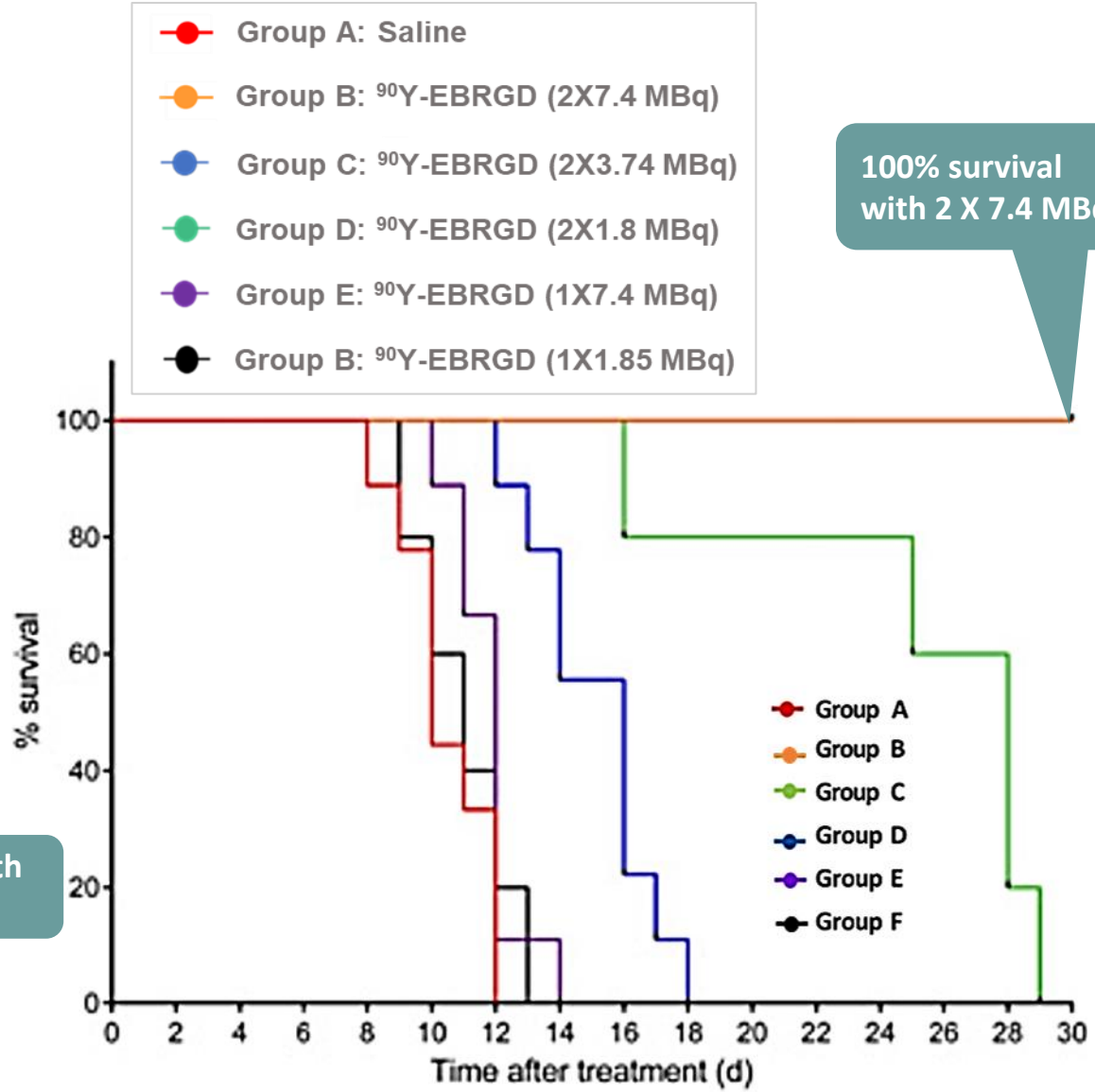


High αvβ3 expressors

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



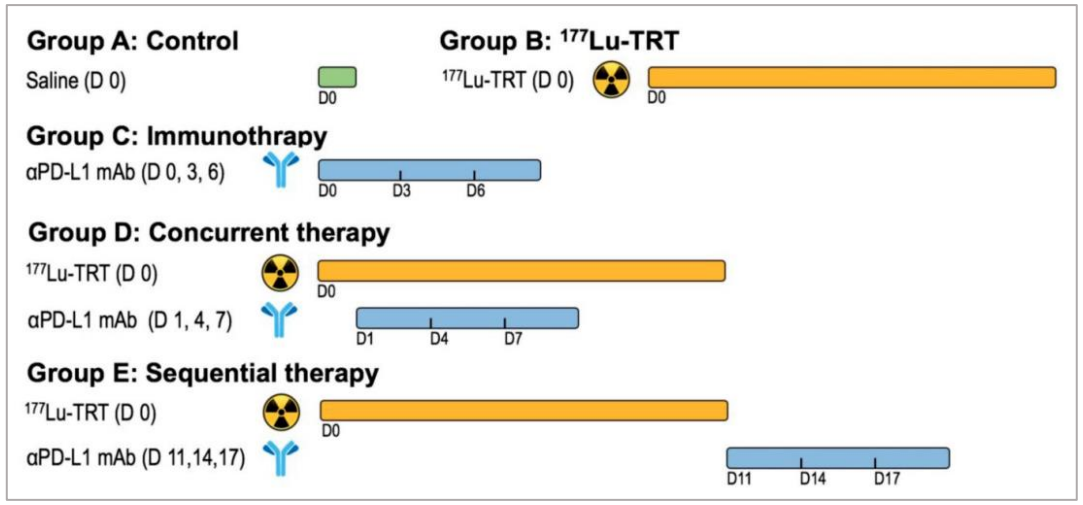
Negligible tumor growth with 2 X 7.4 MBq

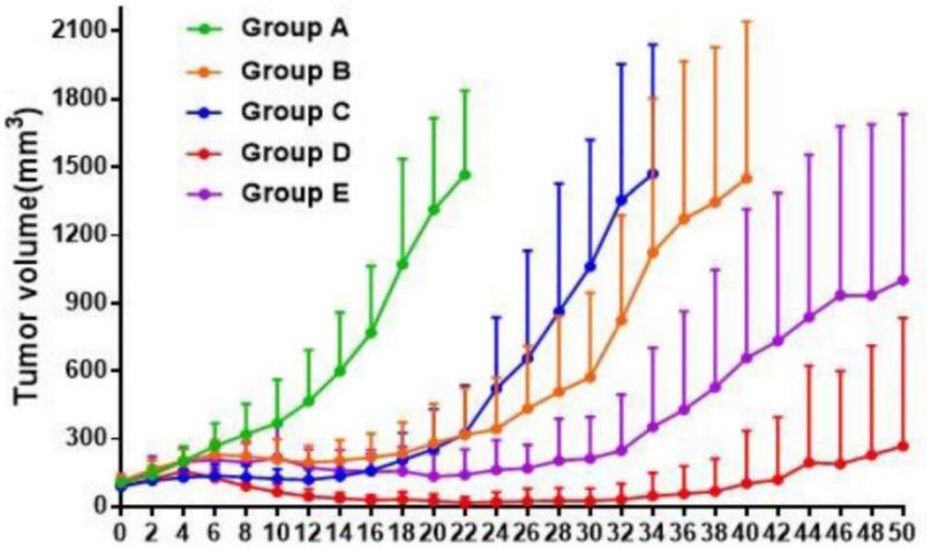


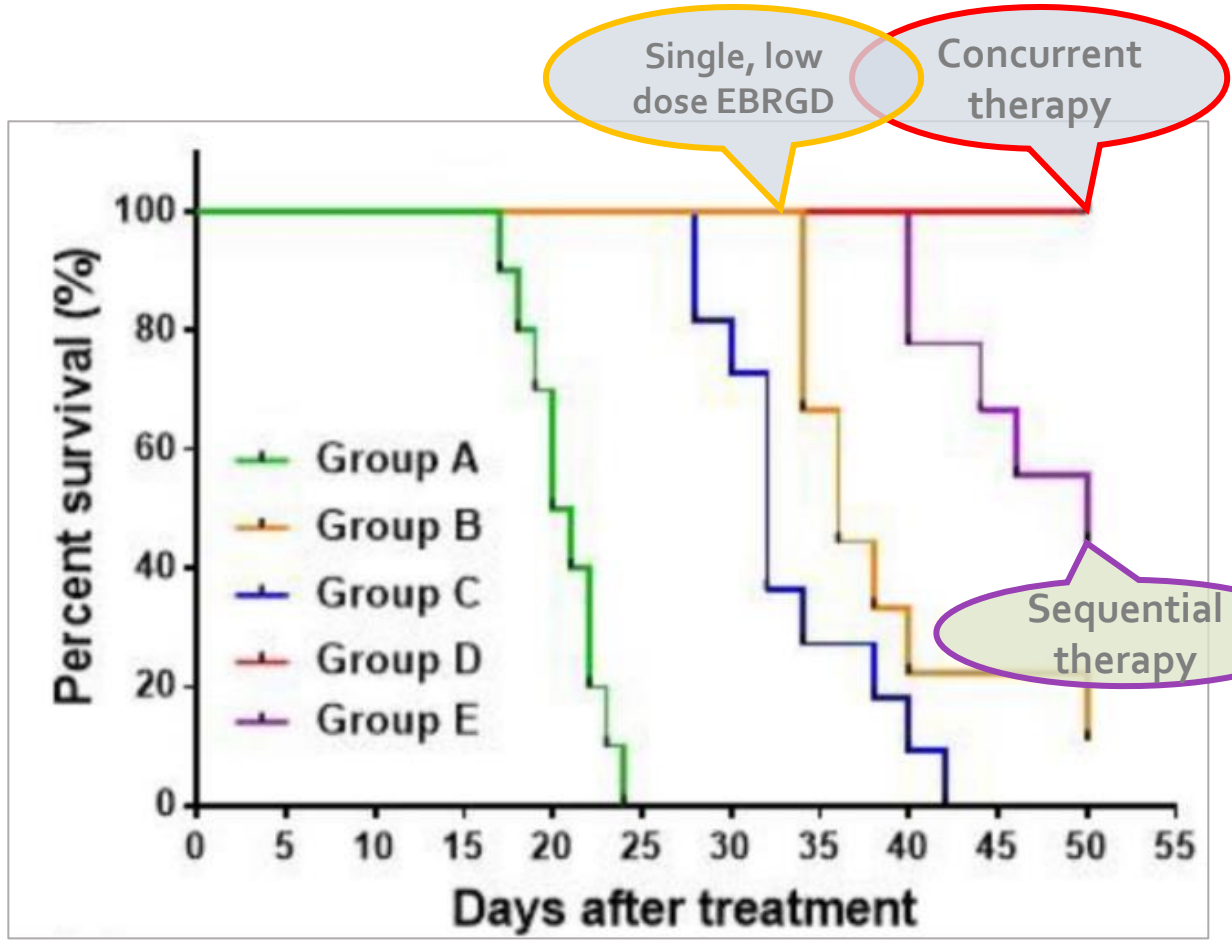
100% survival with 2 X 7.4 MBq

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

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^{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.

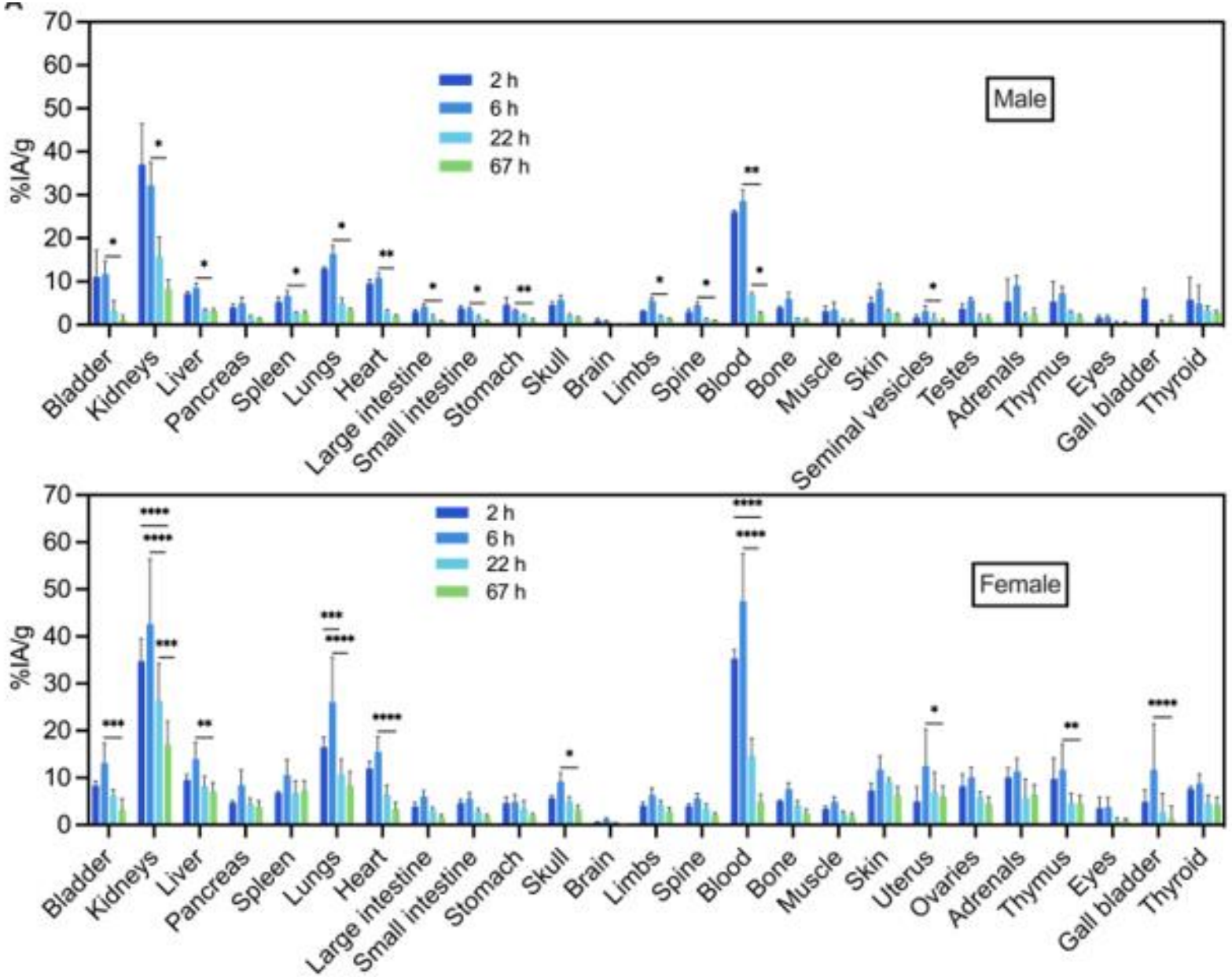
Ther 2020;19:2034–43

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

- Fabrice N. Njotu1, Humphrey Fonge1*et. al,.

Presented in 2024 SNMMI

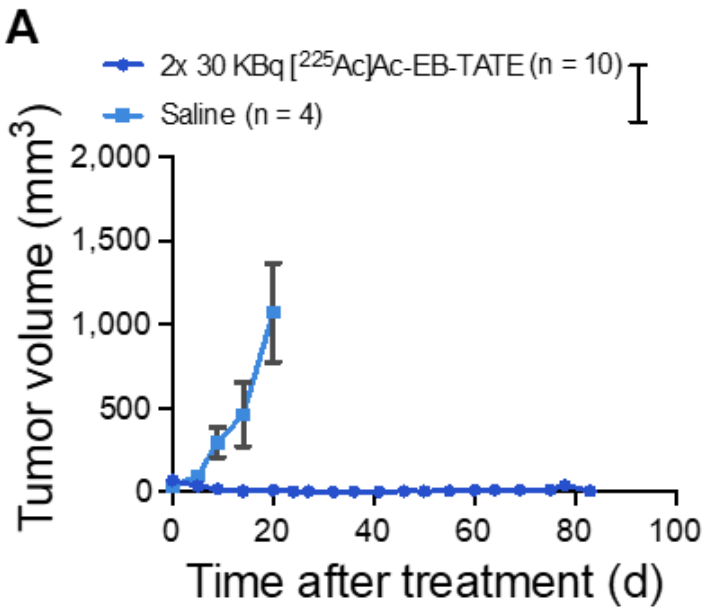
*University of Saskatchewan College of Medicine, Saskatoon, Saskatchewan; and Molecular Targeting Technologies, Inc. West Chester, Pennsylvania



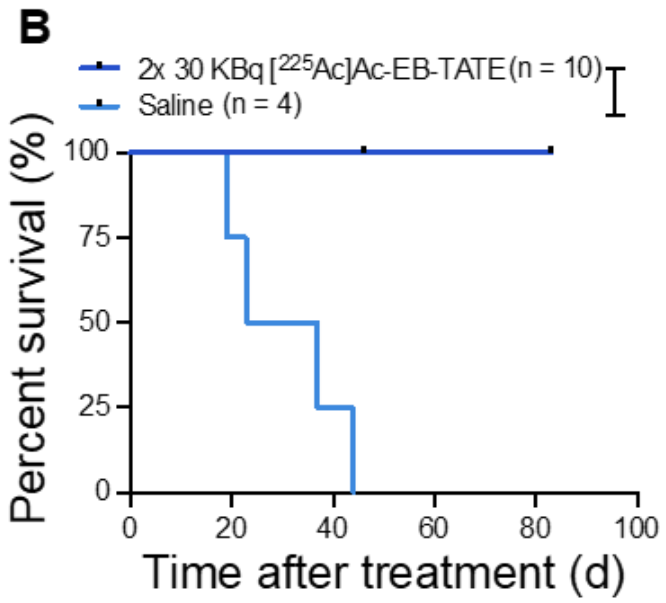
Biodistribution and pharmacokinetic of [^{225}Ac]Ac-EBTATE in healthy BALB/c mice.

Therapy in NCH-H524 (SCLC).

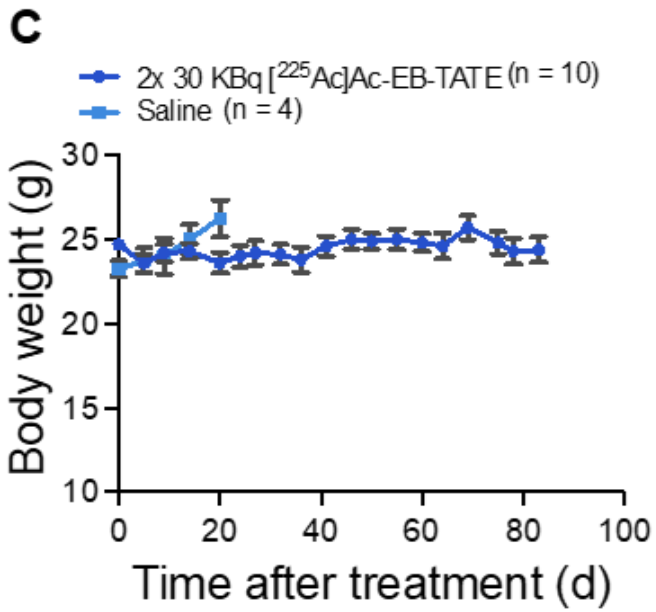
Average tumor growth



Kaplan Meier survival



Average body weights



^{225}Ac-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