MTTI's TARGETED RADIOTHERAPEUTICS:

A NOVEL APPROACH TO SEE AND TREAT CANCER

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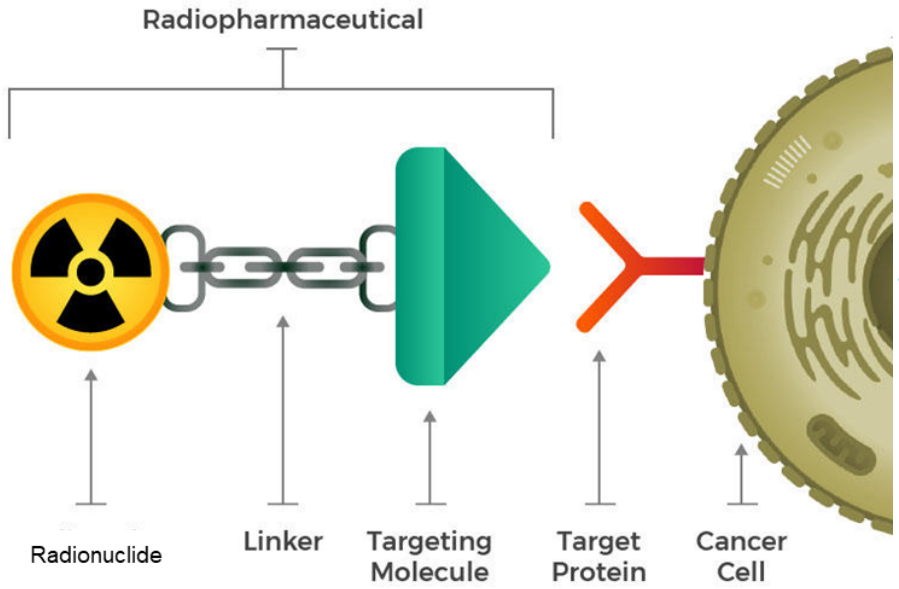
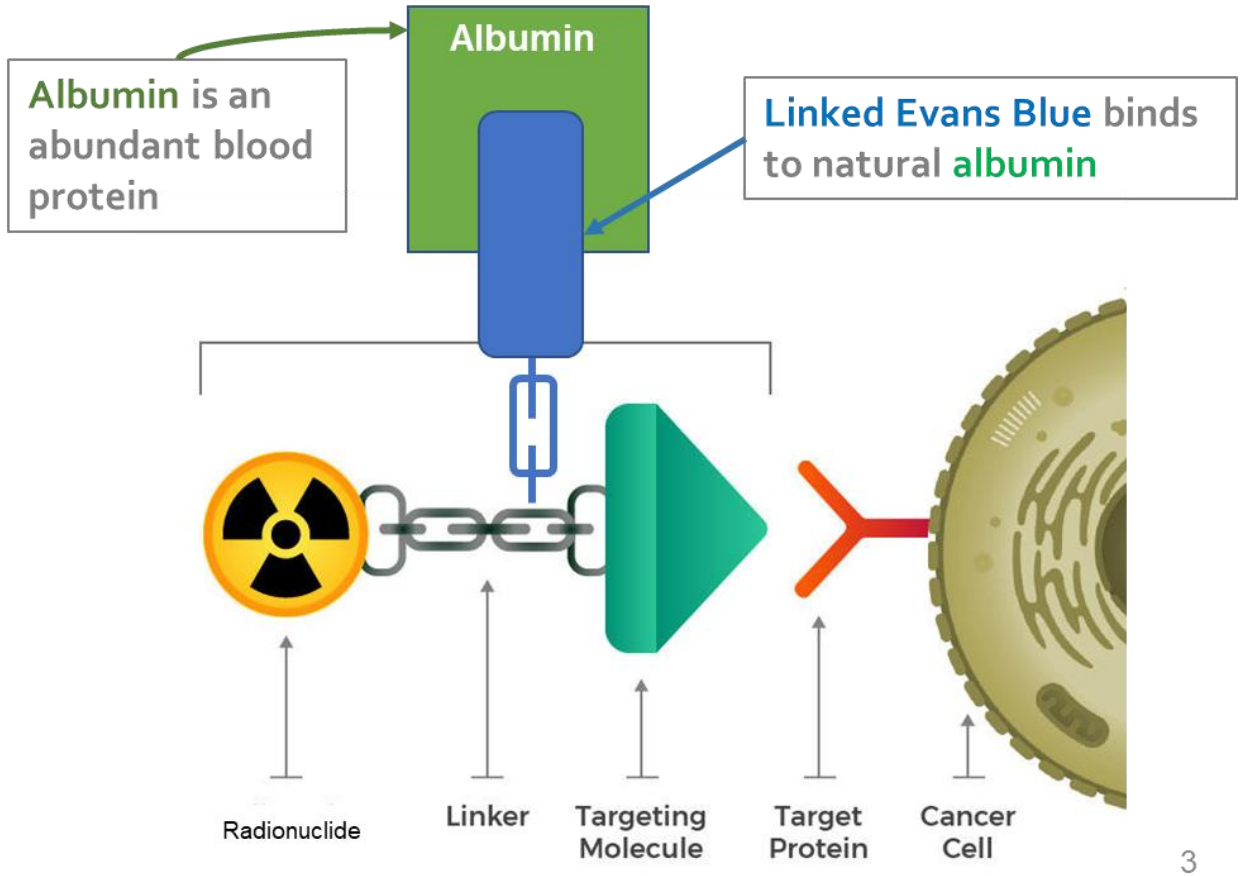
A long-acting, more effective TRT platform

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



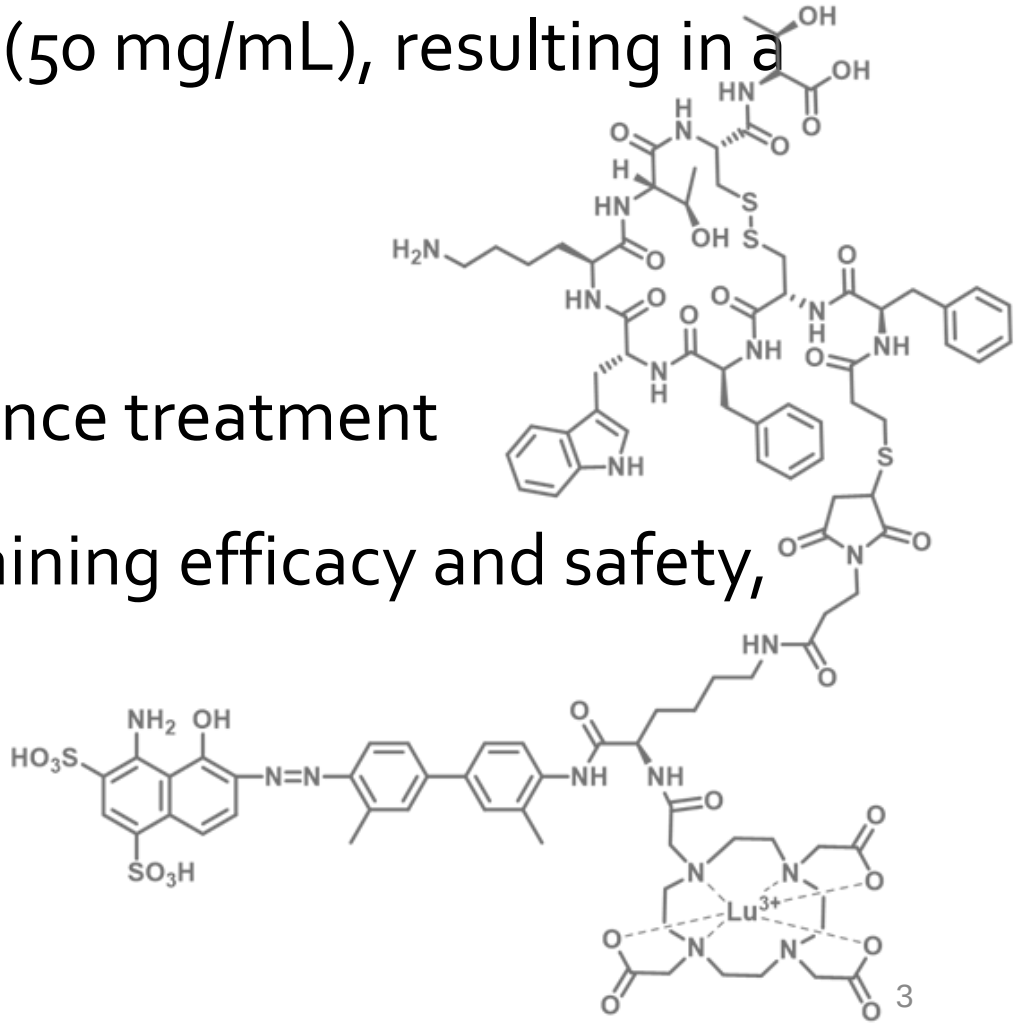
BREAKTHROUGH

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



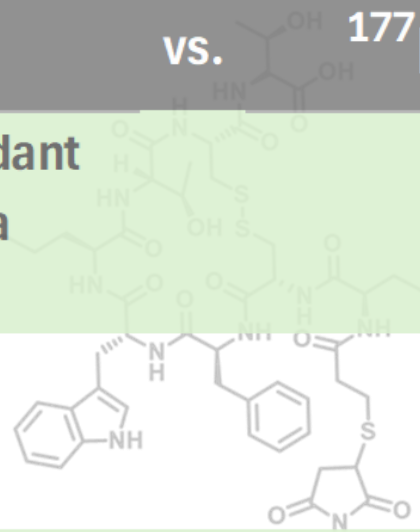
Transforming radiotherapy with an Evans blue (EB) moiety

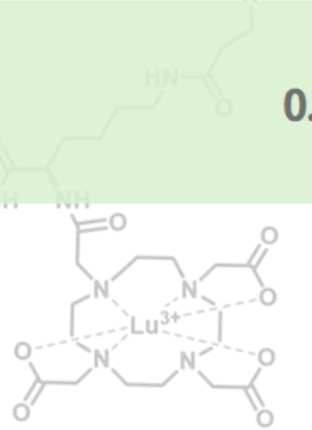
- EB binds to albumin, abundant in the blood (50 mg/mL), resulting in a longer circulatory half-life
- Each albumin binds 8-14 molecules of EB
- Better tissue absorption and retention enhance treatment
- Significantly lower isotope use while maintaining efficacy and safety, improves costs and health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

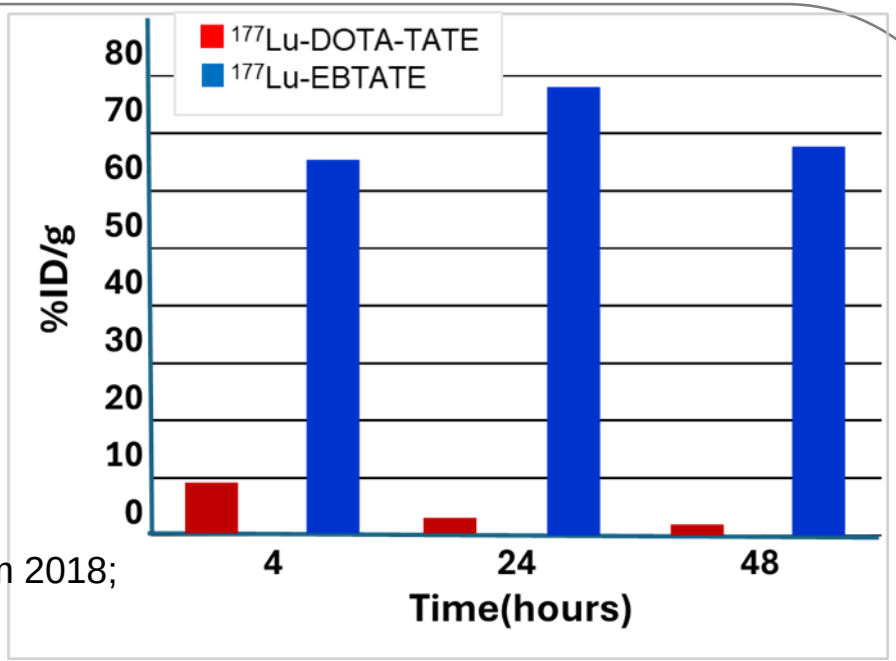




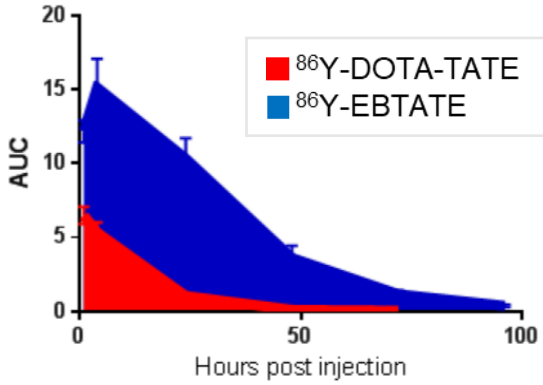
EB impact: Greater retention in AR42J/HCT116 tumor (Preclinical)

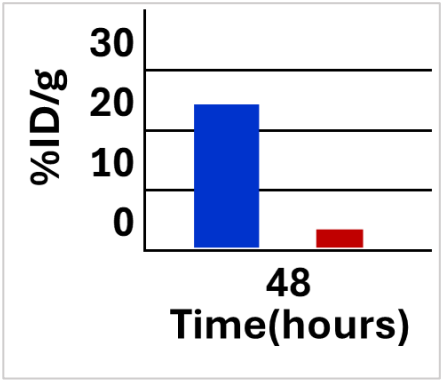
^{177}Lu-EBTATE (78.8% ID/g) vs ^{177}Lu-DOTA-TATE (3%ID/g) at 24 h

AR42J (Pancreatic) SSTR2+ tumor

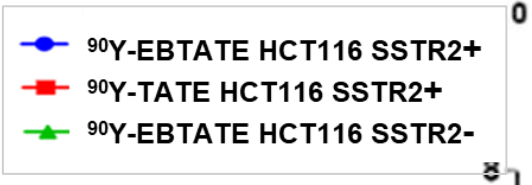


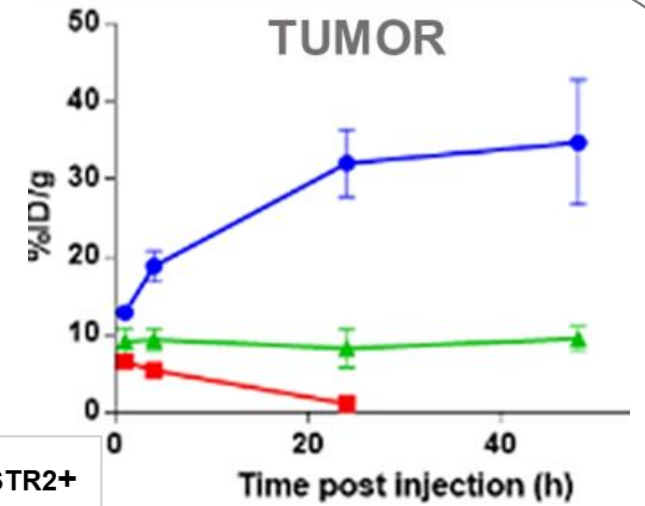
Bioconjugate Chem 2018; 29: 2448-2454

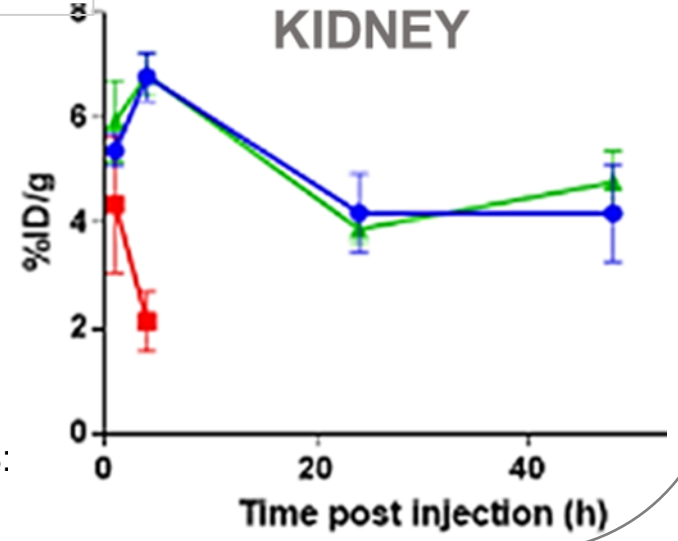




HCT116 (CRC) SSTR2 +/-tumor





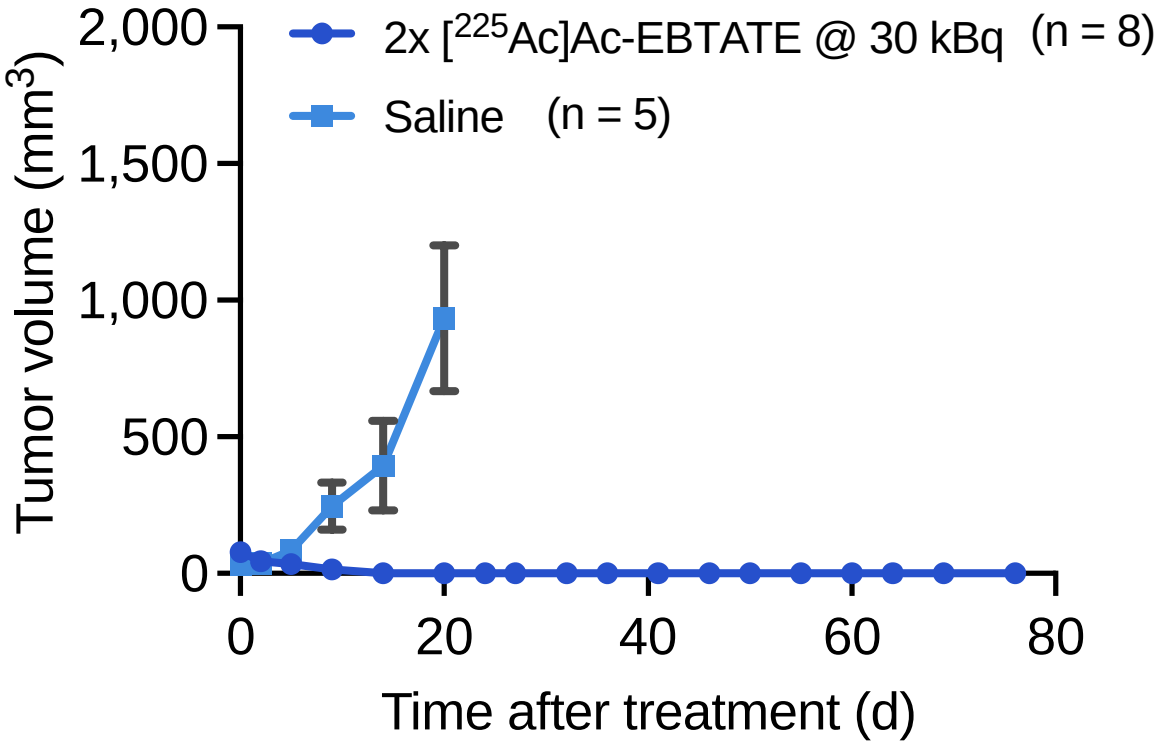


Theranostics 2018; 8: 734-745

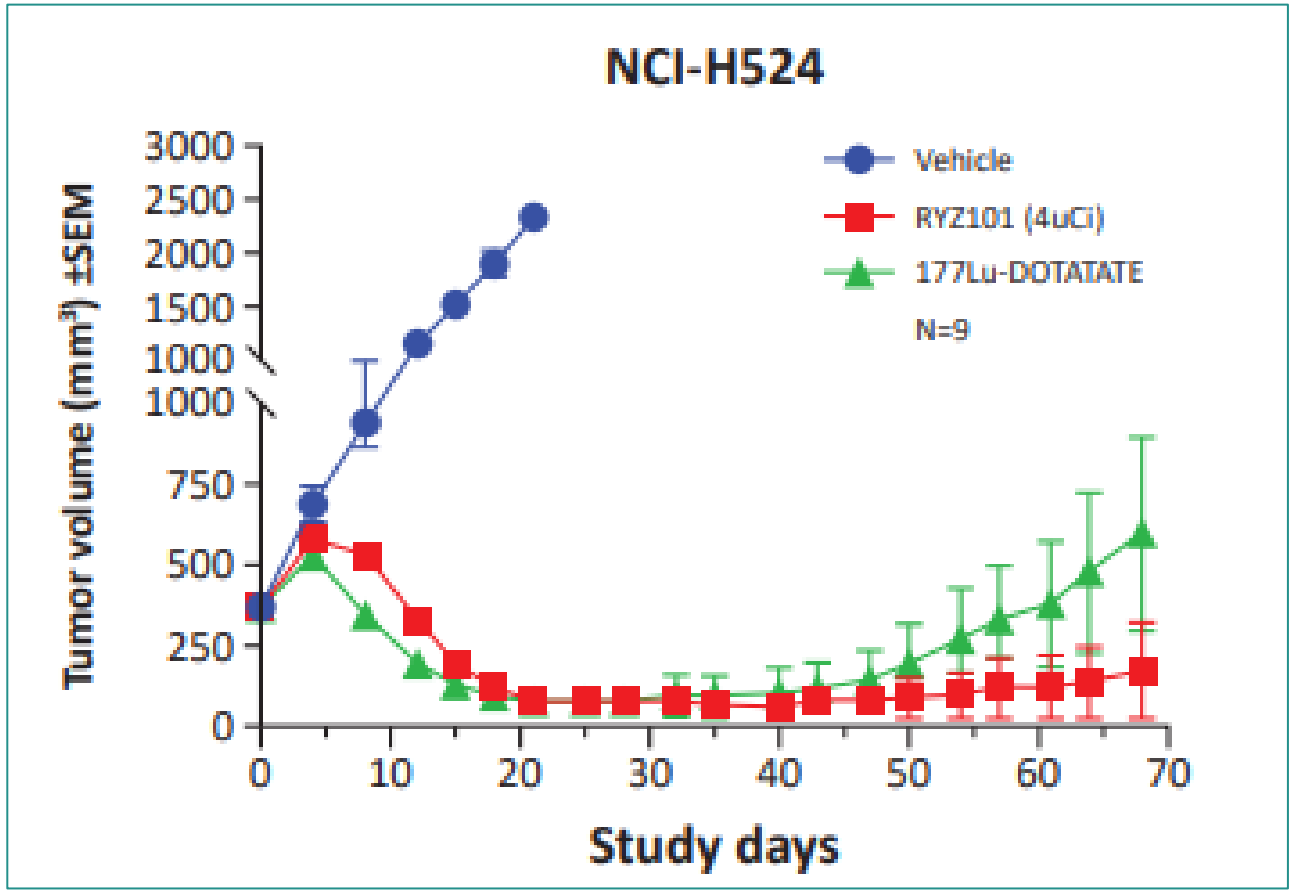
^{225}Ac-EBTATE vs. RayzeBio RYZ101 in SCLC:

similar efficacy at 40% of the RYZ101 dose (BMS acquired RayzeBio for $4.1 B in Dec 2023)

^{225}Ac-EBTATE (2 x 30 kBq)



RYZ101 (148 kBq)

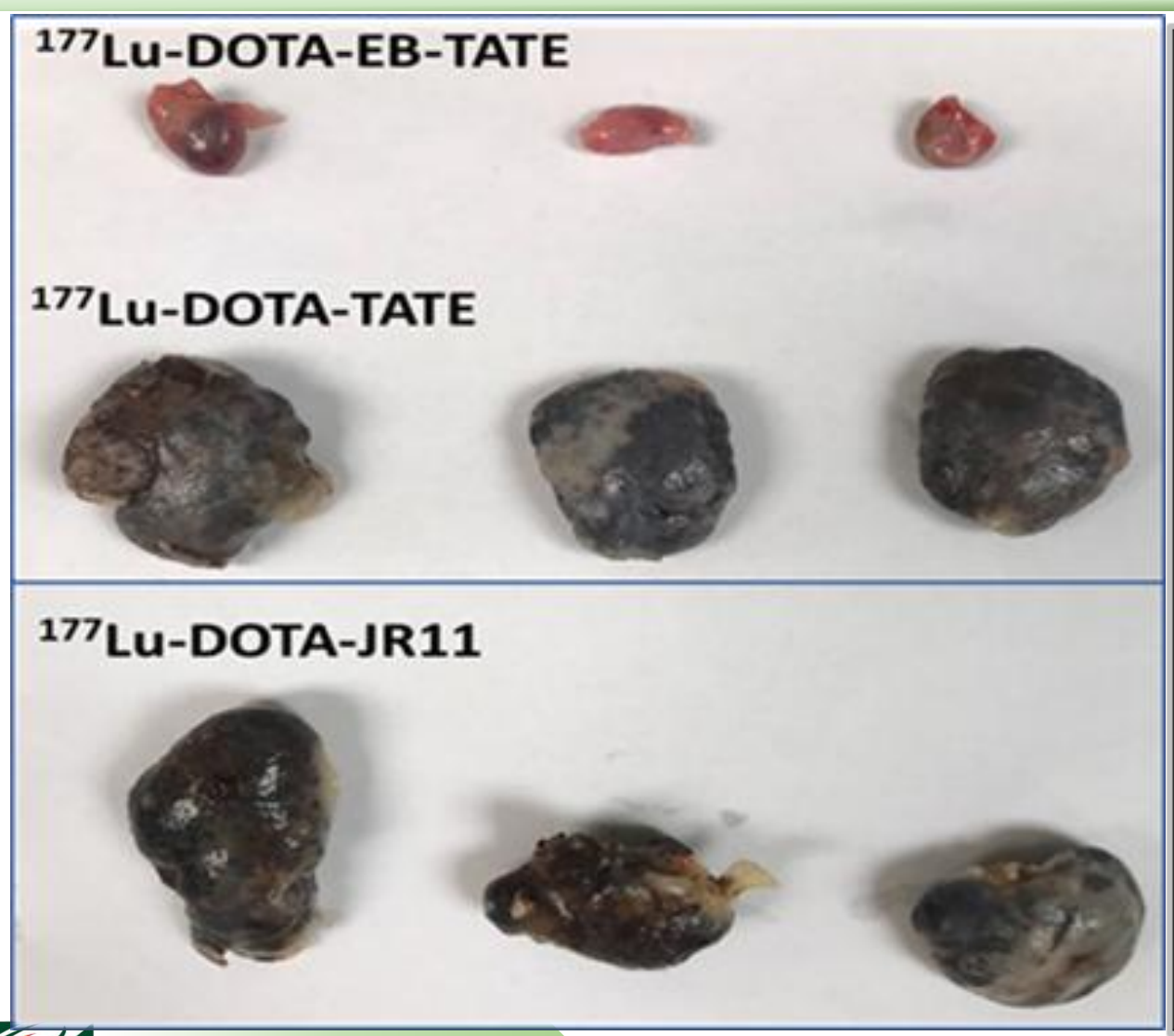


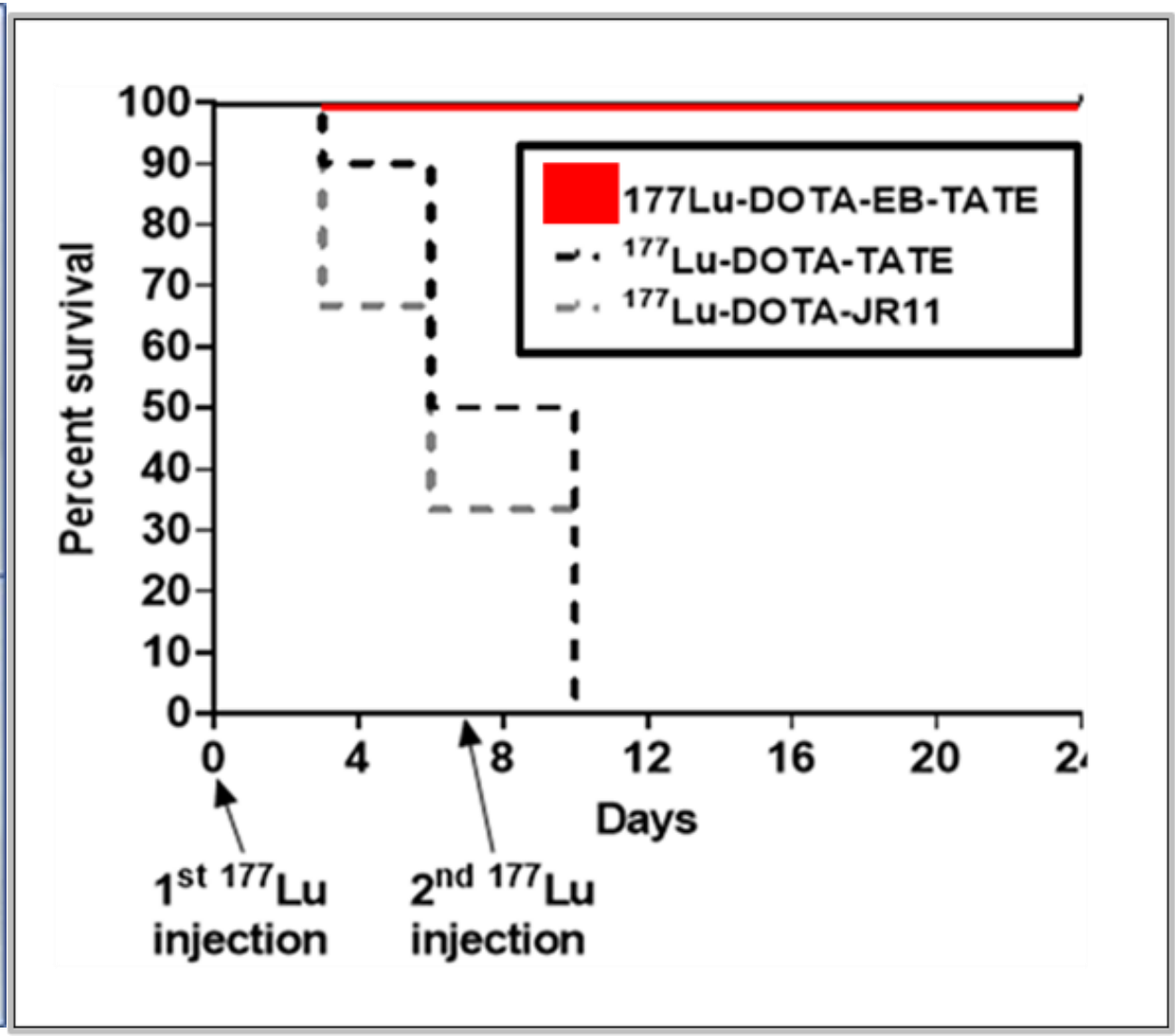
Strategies in increasing retention of TRP at tumor with EB

	Isotope/target	Tumor (cell line/patient)	With EB % ID/g*	No EB %ID/g*	Fold increase
Preclinical	Lu-177/SSTR2	HCT116 (CRC)	78.2	3	26
	Y-86/SSTR2	HCT116 (CRC)	30	1.5	20
	Lu-177/Integrin	Pancreatic (AR42J)	14	3	5
	Cu-64/Integrin	Glioma (U87MG)	16	1	16
Clinical*	Lu-177/SSTR2	NET patient	0.0469±0.0167 MBq h/MBq/g	0.0059±0.0033 MBq h/MBq/g	8

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

^{177}Lu & EBTATE (complete tumor remission) vs. TATE analogs (none remission)

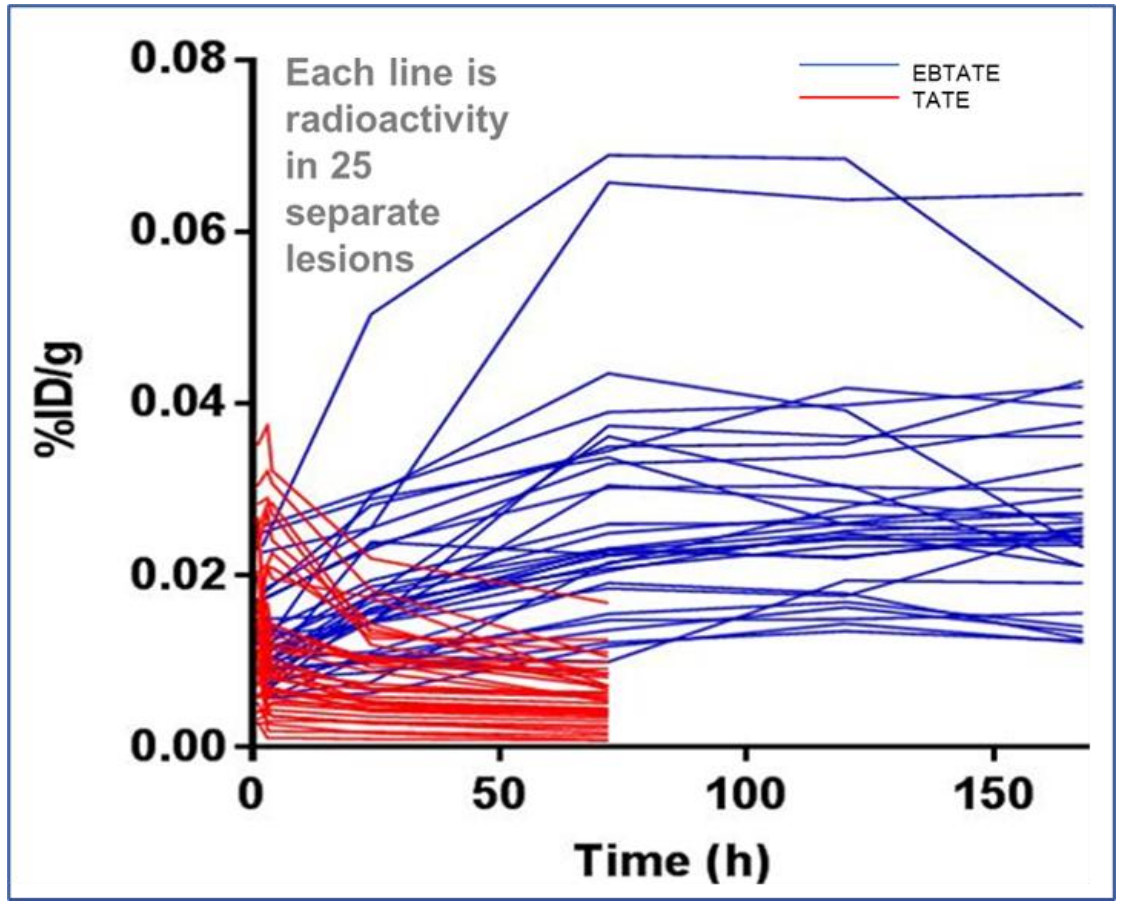




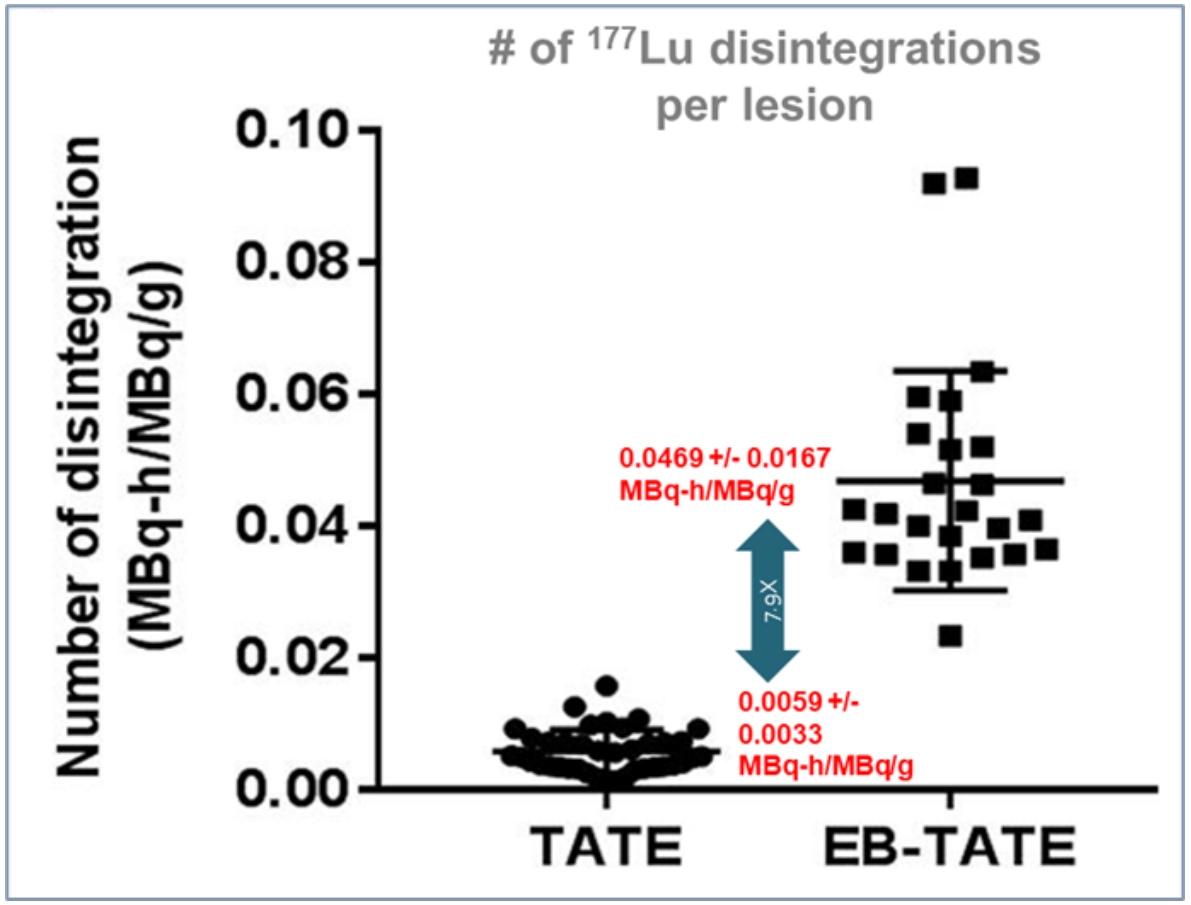
Thakur et al. Clin Cancer Res 2021; 27(5): 1399-1409; Captured in the Best Achievements in Clinical Thyroidology as NOVEL THERAPEUTICS. Endocrinol Metab 2021;36:30-35*

EB improves PK/PD in patients

EBTATE sustained tumor absorption in NET patients

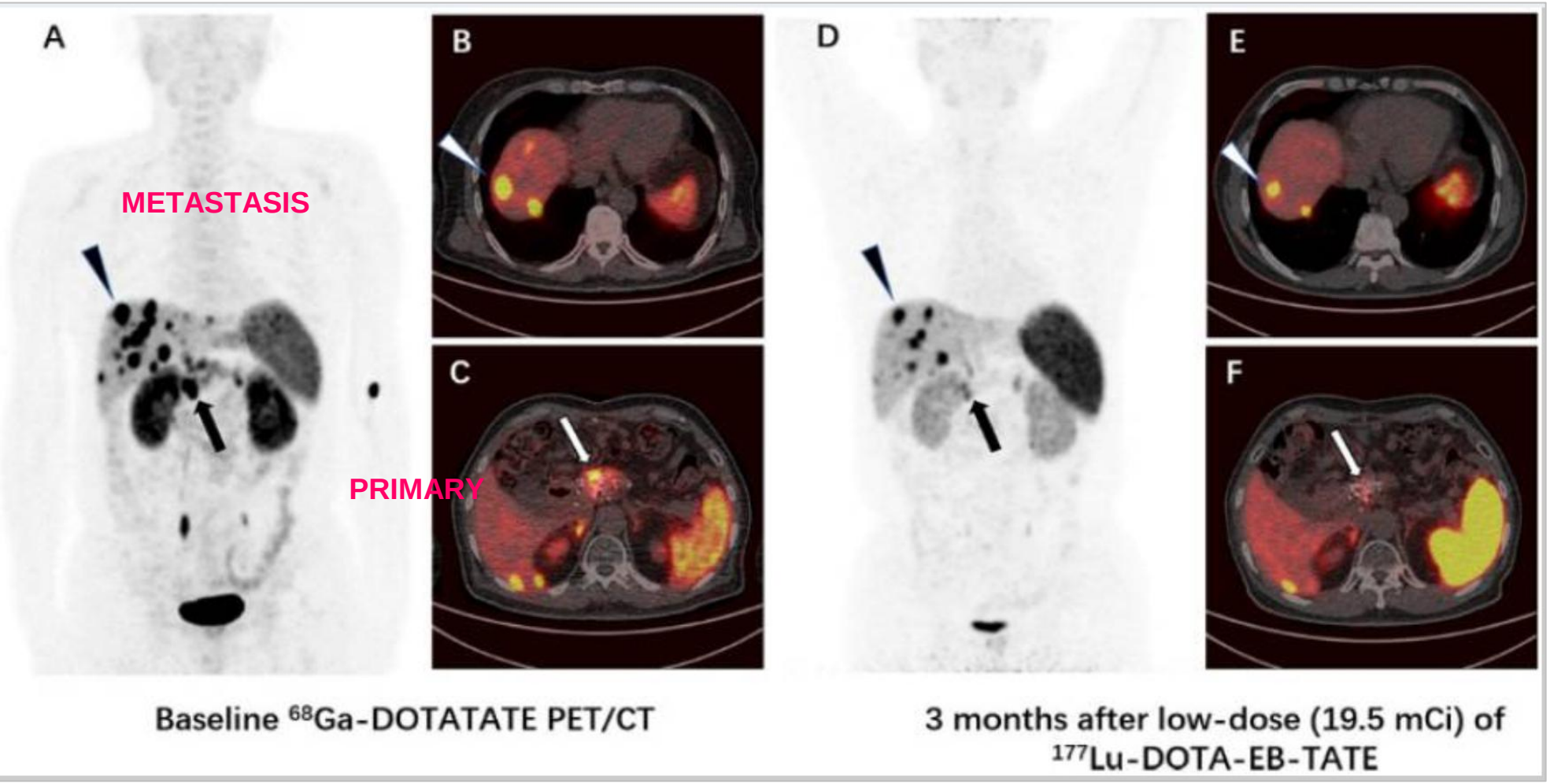


EBTATE shows a 7.9-fold tumor radiation count increase vs 177Lu-DOTA-TATE



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

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



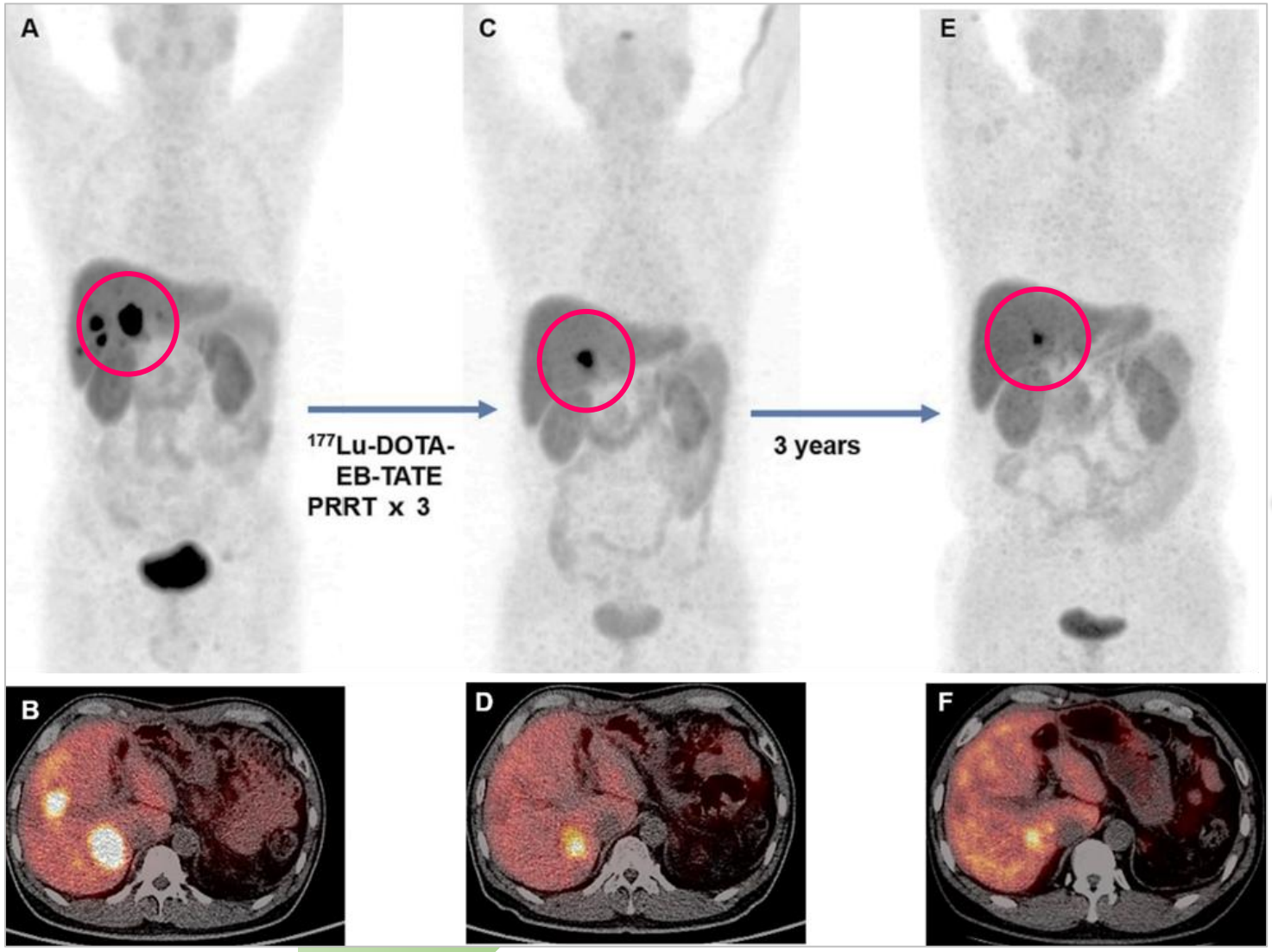
^{68}Ga-DOTA-TATE/CT images before and after EBTATE injection:
(A-C)-prior to EBTATE
(D-F)-after EBTATE

SUVmax at the primary tumor dropped from 26.7 to 13.0 (arrow), uptake of SUVmax of metastasis dropped from 50.6 to 28.6 (triangle) (DEF).

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	

Evans blue (EB) Advantages - transforming radiotherapy

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

Summary: **Transforming radiotherapy with Evans blue(EB)**

- 8-fold greater retention in NET patients using ^{177}Lu-EBTATE than with ^{177}Lu-DOTA-TATE and early studies indicated ^{177}Lu-EBTATE without amino acids infusion did not affect kidney functions

- Greater retention at 78.8% ID/g using ^{177}Lu-EBTATE vs 3% ID/g with ^{177}Lu-DOTA-TATE at 24 h in HCT116 CRC tumor model. Complete tumor remission using ^{177}Lu /^{90}Y EBTATE vs. TATE analogs (none remission) in AR42J, pancreatic cancer mouse model

- ^{225}Ac-EBTATE showed 80% complete remission, 100% survival in in NCH-H524 (Small cell lung cancer model)

MTTI Pipeline – Focus on radiopharmaceuticals

PRODUCT	TARGET	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
THERAPEUTICS						
Lu-177-EBTATE	SSTR2	Neuroendocrine tumors	completed60+ pts		Showed safety & efficacy	Published PUMC
		Neuroendocrine tumors	Phase 1 25			MSKCC
		Hürthle Cell Thyroid cancer	Phase 1/2 H2 25′			Funded by NIDDK
		Nasopharyngeal cancer	Phase 1/2 H2 25′			
Ac-225-EBTATE	SSTR2	NET/SCLC	Phase 1/2 H2 25′			
Lu-177-EBRGD	αvβ3 Integrin	αvβ3+ solid tumors	IND H2 25′			Funded by NCI
		αvβ3+ brain tumors				
DIAGNOSTICS						
CypH-11 Spray	NIR guided surgery	Ovarian/Peritoneal cancer	IND H1 26′			Funded by NCI

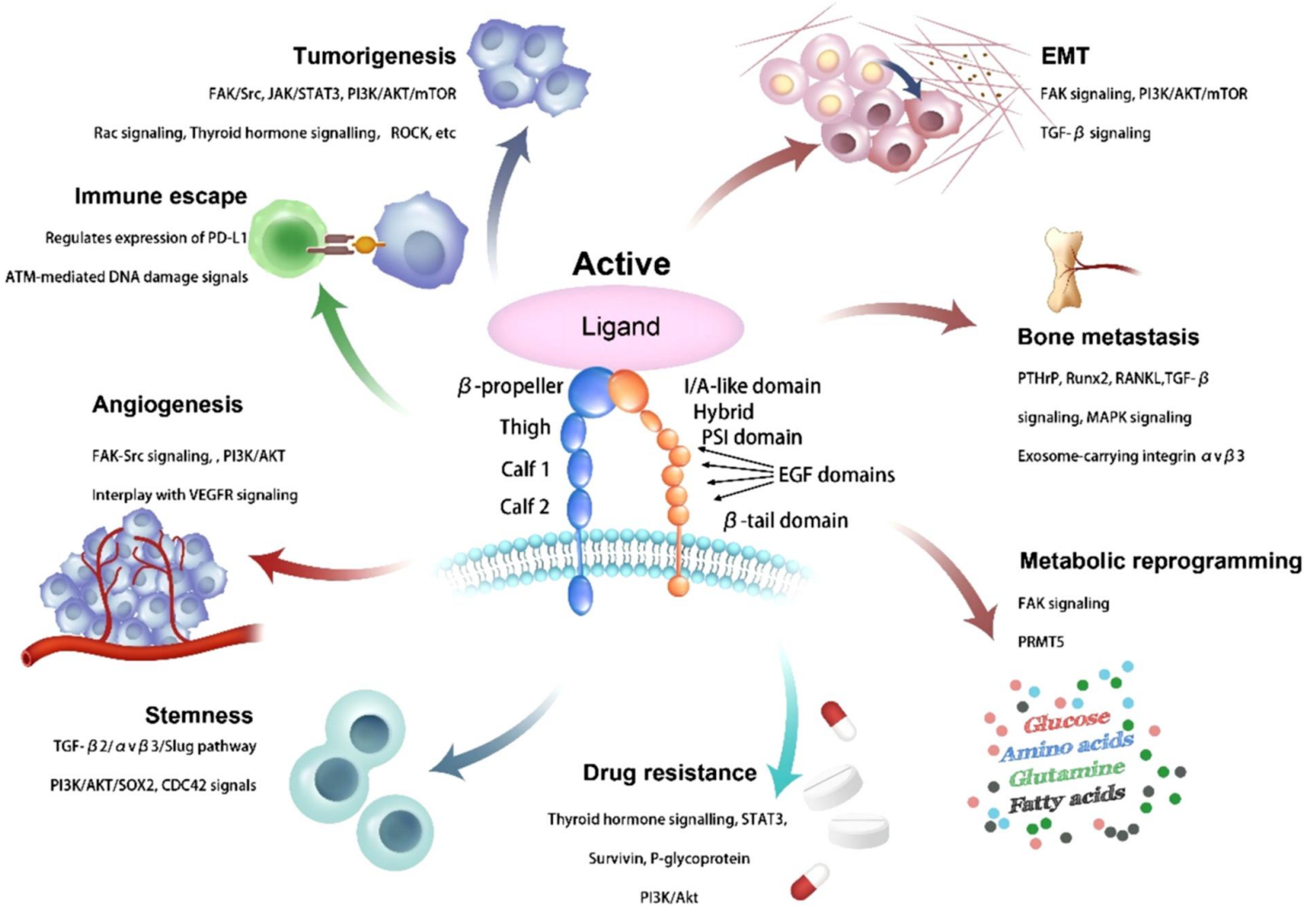
NCI: National Cancer Institute; NIDDK: National Institute of Diabetes, Digestive and Kidney Diseases:

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.

RGD-based PET tracers detect most αvβ3 metastases in cancers

SUVs at tumor site using RGD-based PET without EB

Tracer name	Patient number	Tumor type	Detection rate (Sensitivity)	SUVs
[^{18}F]Galacto-RGD	8	**5 Melanomas** **2 Sarcomas** **1 RCC**	6/7 (86%), primary lesion 1/1 (100%), distant metastases 7/8 (88%), all lesions	1.2-10.0
[^{18}F]Galacto-RGD	19	**10 Musculoskeletal** **4 Melanoma** **2 SCCHN** **2 GBM** **1 Breast cancer**	17/19 (89%), primary lesion	1.2-10.0
[^{18}F]Galacto-RGD	11	**11 SCCHN**	10/12 (83%), primary lesion 2/6 (33%), lymph nodes 12/18 (67%), all lesions	2.2-5.8
[^{18}F]Galacto-RGD	16	**10 NSCLC** **2 RCC** **1 SCCHN** **1 Rectal cancer** **1 Breast cancer**	13/14 (93%), primary lesion 7/13 (54%), lymph nodes 25/32 (78%), metastases 45/59 (76%), all lesions	0.3-6.8
[^{18}F]Galacto-RGD	12	**12 GBM**	11/12 (92%), primary lesion	0.8-2.8
[^{18}F]Galacto-RGD	16	**16 Breast cancer**	12/12 (100%), primary lesion 3/8 (38%), lymph nodes 11/24 (46%), metastases 26/44 (59%), all lesions	1.4-8.7

Tracer name	Patient number	Tumor type	Detection rate (Sensitivity)	SUVs
[^{18}F]Fluciclatide	7	**7 Breast cancer**	1/1 (100%), primary lesion 15/17 (88%), metastases 16/17 (94%), all lesions	1.4-40.0
[^{18}F]Fluciclatide	17	**11 RCC** **6 Melanoma**	10/10 (100%), primary lesion 5/7 (71%), metastases	1.8-10.0
[^{18}F]RGD-K5	12	**Breast cancer**	15/17 (88%), all lesions 122/157 (77.7%), all lesion	
[^{18}F]FPPRGD2	8	**Breast cancer**	8/8 (100%), primary lesion 4/5 (80%), lymph nodes 17/17 (100%), metastases 29/30 (97%), all lesions	2.4-9.4
[^{18}F]FPPRGD2	15	**Recurrent GBM**	17/17 (100%), primary lesion	0.8-5.8
[^{18}F]Alfatide	9	**NSCLC**	9/9 (100%), primary lesion	2.91±0.73
[^{18}F]Alfatide II	30	**Bone metastases**	100%, osteolytic metastases 70%, osteoblastic metastases 100%, mixed bone metastases 98%, bone marrow metastases 92%, all metastases	0.95-13.87
[^{18}F]Alfatide II	9	**Brain metastases**	20/20 (100%), brain metastases	1.8-10.0
[^{68}Ga]NOTA-PRGD2	12	**Glioma**	10/12 (83.3%), primary lesion	0.5-2.31

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Theranostics 2016; 6(1): 78-92.

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

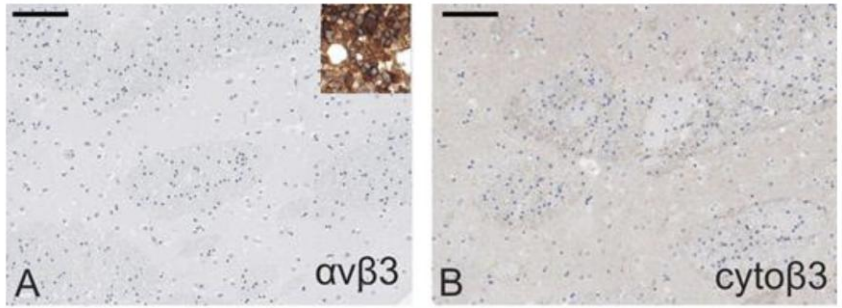
*Boger et al. Virchows Arch. 2014;464(1):69-78.; Echavidre et. al., Pharmaceutics. 2022;14(5):1053;
Jin et al. PLoS One. 2012;7(10):e48575, Kariya et. al. Comm Biol 2021;4:490.

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

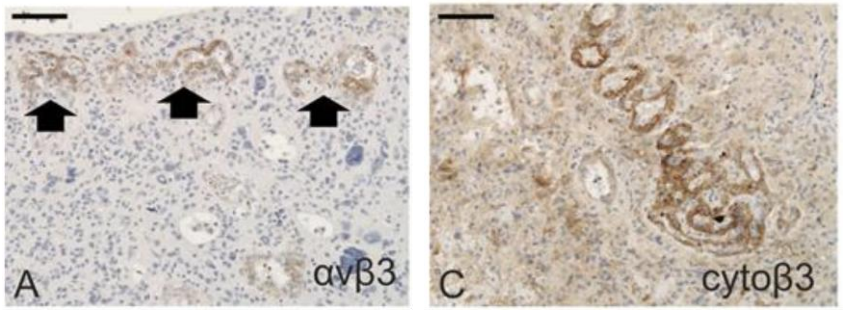
- αvβ3 integrin has – **low or no expression in normal tissues, overexpressed in many tumors**
- **RGD based PET tracer detects 100% primary lesions in cancer**
- αvβ3 was found in **neovascular** cells and **tumor cells**

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

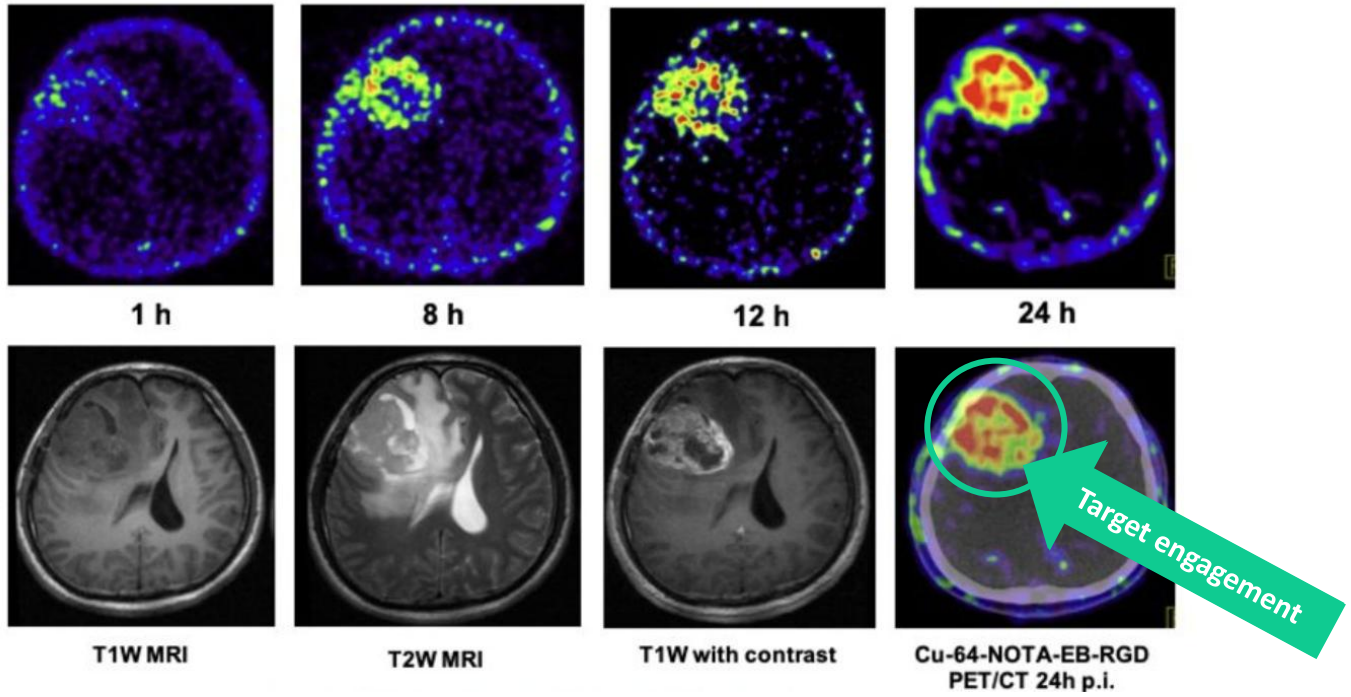


	αvβ3 positive tissues
Normal brain	0/78
Glioblastoma (WHO IV)	86/160

*Schittenhelm 2013, Echavidre 2022

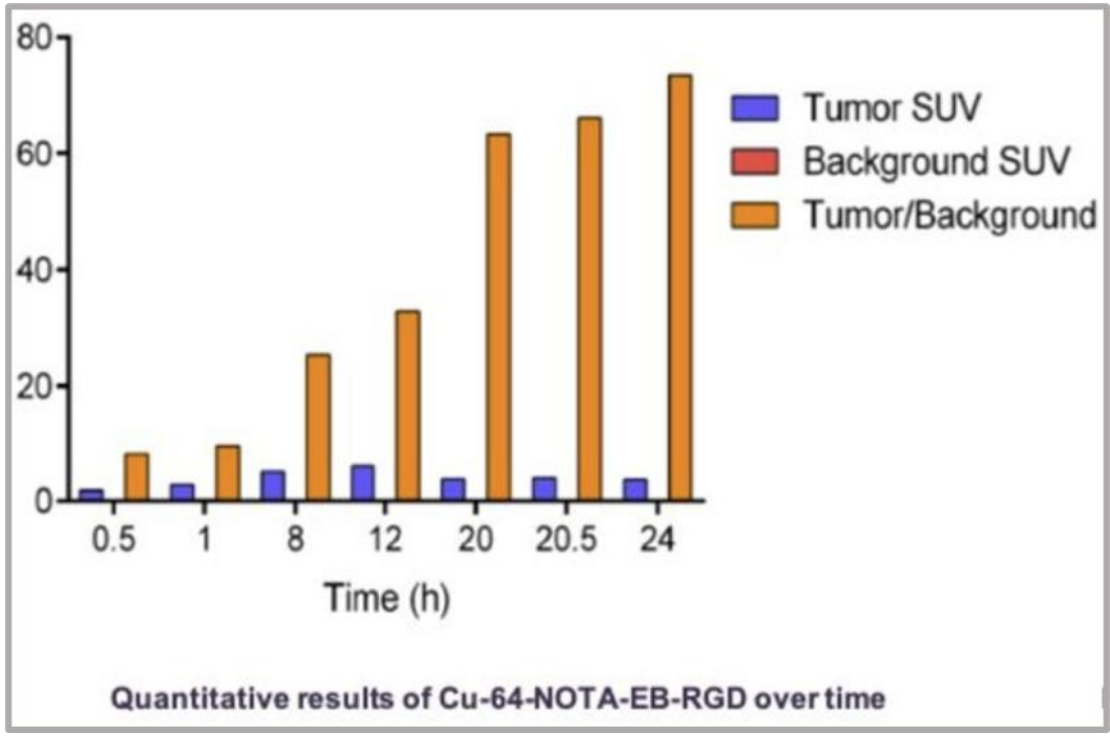
^{64}Cu-EBRGD – robust target engagement in GBM patients

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

Is residence time important?

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
- A validated target, αvβ3, has been studied in the past
- Proposed rationale for the failure:
  - Signaling based therapy is not potent enough to kill cancer cells
  - Short residence time is insufficient

Evans blue may overcome this challenge

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)

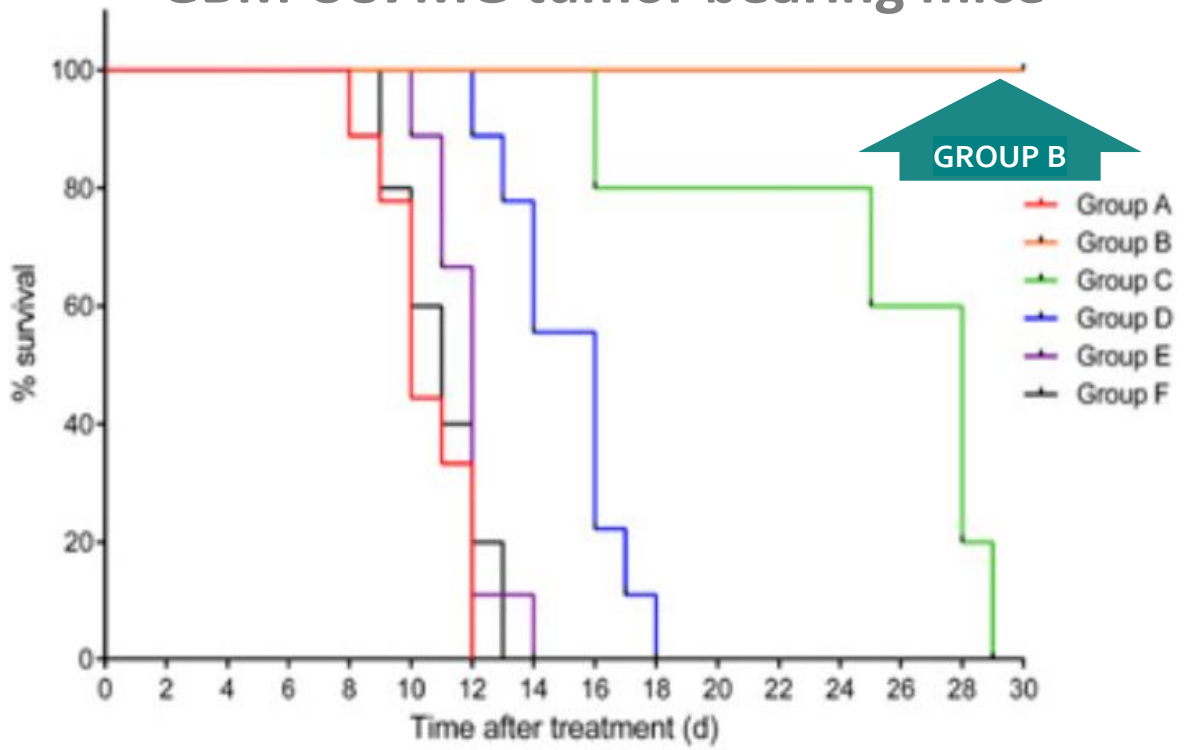
- FF58 is an αvβ3 and αvβ5 dual targeting molecule without the albumin binding motif

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)

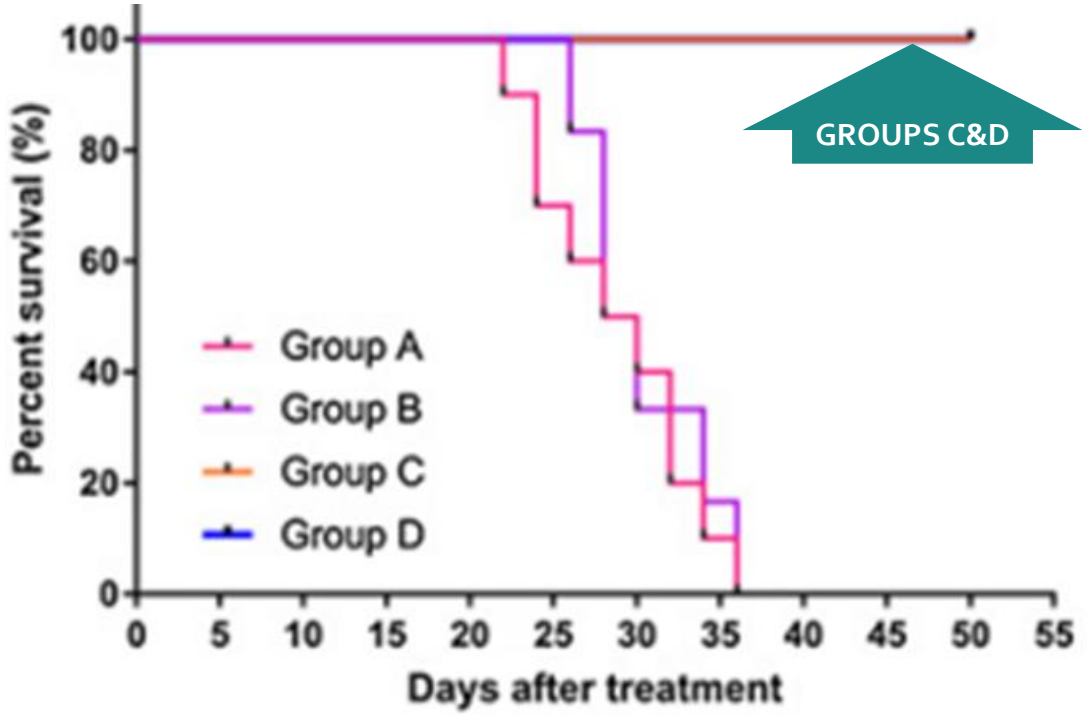
^{177}Lu & ^{90}Y EBRGD vs. RGD analogs

GBM U87MG tumor bearing mice



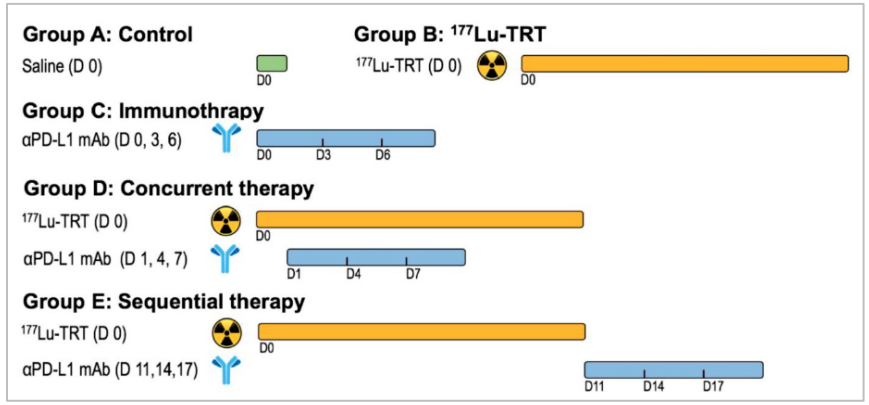
Group A: : saline
Group B: ^{90}Y-EBRGD (2x 7.4 MBq)
Group C: ^{90}Y-EBRGD (2X 3.7 MBq)
Group D: ^{90}Y-EBRGD (1X 1.85 MBq)
Group E: ^{90}Y-RGD (1X 7.4 MBq)
Group F: ^{90}Y-RGD (1X 1.85 MBq)

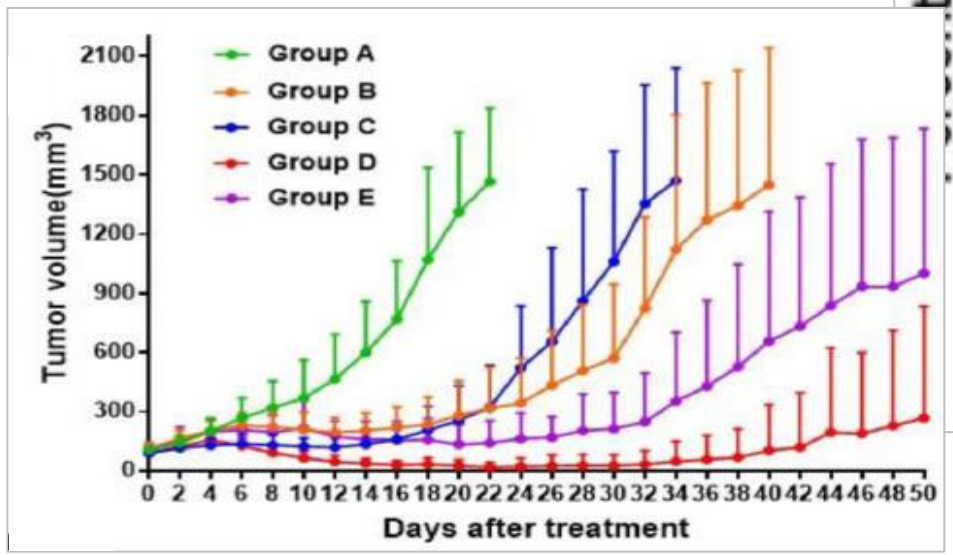
NSCLC-PDX BALB/c nude mice

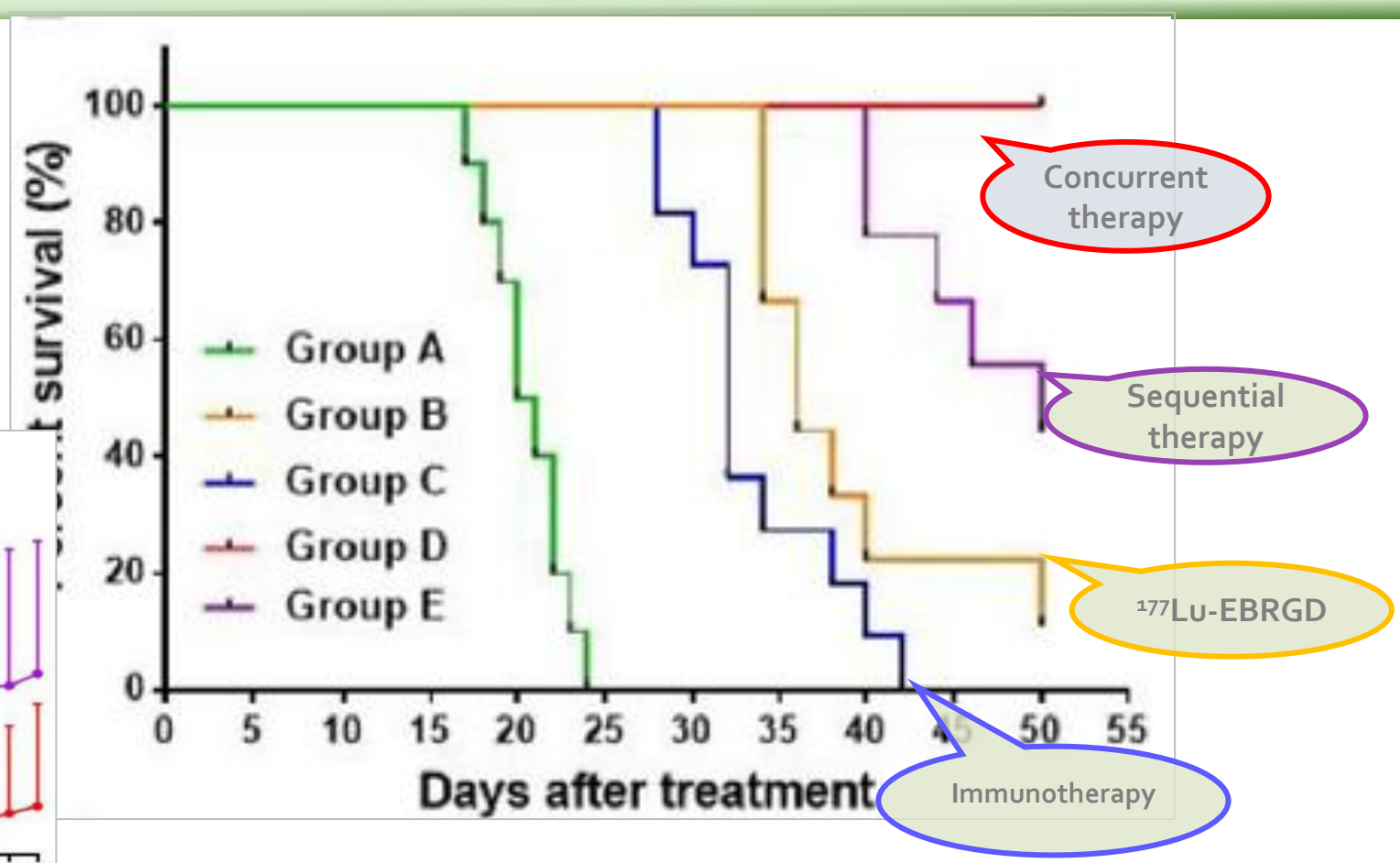


Group A: : saline
Group B: ^{177}Lu-RGD (29.6mBq)
Group C: ^{177}Lu-EBRGD (18.5mBq)
Group D: ^{177}Lu-EBRGD (29.6mBq)

^{177}Lu-EB-RGD had synergistic effect with immunotherapy in a colorectal cancer model







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

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

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