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Molecular Targeting Technologies, Inc.
Advancing Precision Pharmaceuticals

Molecular Targeting Technologies, Inc.

Advancing Precision Medicines – Transforming the lives of patients burdened with severe and life-threatening diseases

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PIPELINE

PRODUCT	TARGET	INDICATION	PRECLIN	PHASE I	PHASE II	PHASE III
THERAPEUTICS						
Rabies mAb	Rabies antigen	Rabies	OUTLICENSED - LAUNCHED			
BPRDP056	Phosphatidylserine	Multiple cancers	OUTLICENSED			
EBTATE™	SSTR2	Neuroendocrine tumors				
	SSTR2	Hürthle Cell Thyroid cancer	PHASE I/II			
	SSTR2	Nasopharyngeal cancer	PHASE I/II			
EBRGD™	integrin $\alpha v \beta_3$	Non-small cell lung cancer				
	integrin $\alpha v \beta_3$	Glioblastoma Multiforme				
ExoBlock	Phosphatidylserine	Advanced melanoma immunotherapy				
DIAGNOSTICS						
^{99m}Tc-glucarate	Cell death	Misc. cancers, cardiac trauma				
TDURA	Cell death	Colorectal cancer				
^{18}F-fluoroglucaric acid	Cell death	Misc. cancers, cardiac trauma				
CypH-11 Spray	NIR guided surgery	Ovarian/Peritoneal cancer				
PSVue-Eye Drops	Cell death	Ocular diseases				

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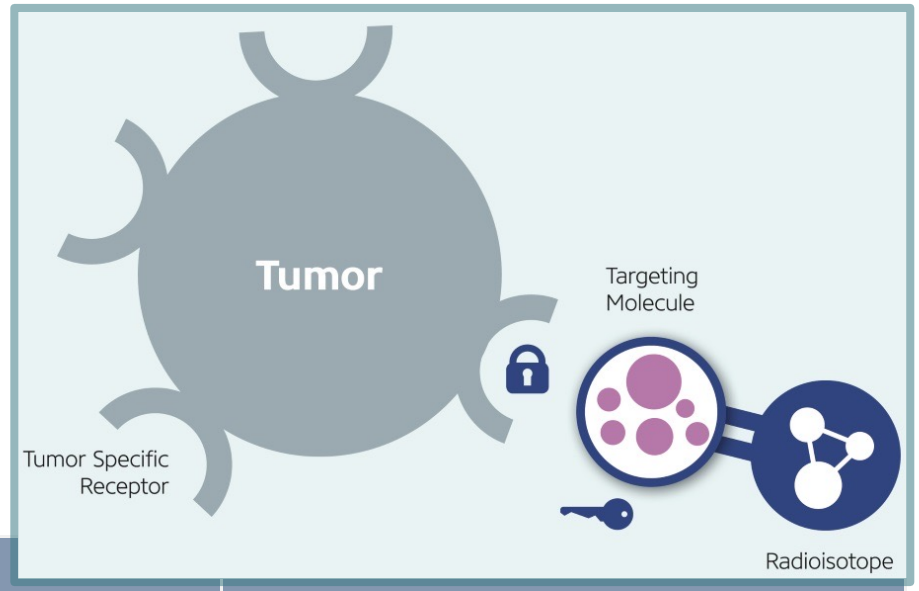
EvaThera™ Platform

Peptide Receptor Radionuclide Therapy (PRRT)



PLATFORM DRUG	PROBABLE INDICATIONS	TARGET RECEPTOR (high tumor density vs. normal organ expression)	LIGAND (agonist/antagonist/inhibitor, affinity/specificity, metabolic stability)	RADIONUCLIDES (emission)
EBTATE	NET, Hurthle cell thyroid, nasopharyngeal, pancreatic, renal and others	Somatostatin receptor type 2 (SSTR-2)	TATE - agonist, high affinity, high specificity, stable	^{177}Lu [low energy, short range (2.2mm) beta particle] ^{225}Ac [very high energy, very short range (40-100µm), alpha particle]
EBRGD	Targets glioblastoma multiforme, non-small cell lung, ovarian, breast, bone, prostate & others. Enhances immunotherapy efficacy.	$\alpha_v\beta_3$ integrin	RGD - inhibitor, high affinity, high specificity, stable	^{177}Lu [low energy, short range (2.2mm) beta particle] ^{225}Ac [very high energy, very short range (40-100µm), alpha particle]

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EvaThera™ Theranostics

MTTI's radiotherapeutic/radiodiagnostic platform

EBTATE™ (^{177}Lu-DOTA-EB-TATE)

Targeted peptide radiotherapeutic for SSTR2 expressing tumors

Peptide Receptor Radionuclide Therapy (PRRT) – ^{177}Lu–DOTA–TATE

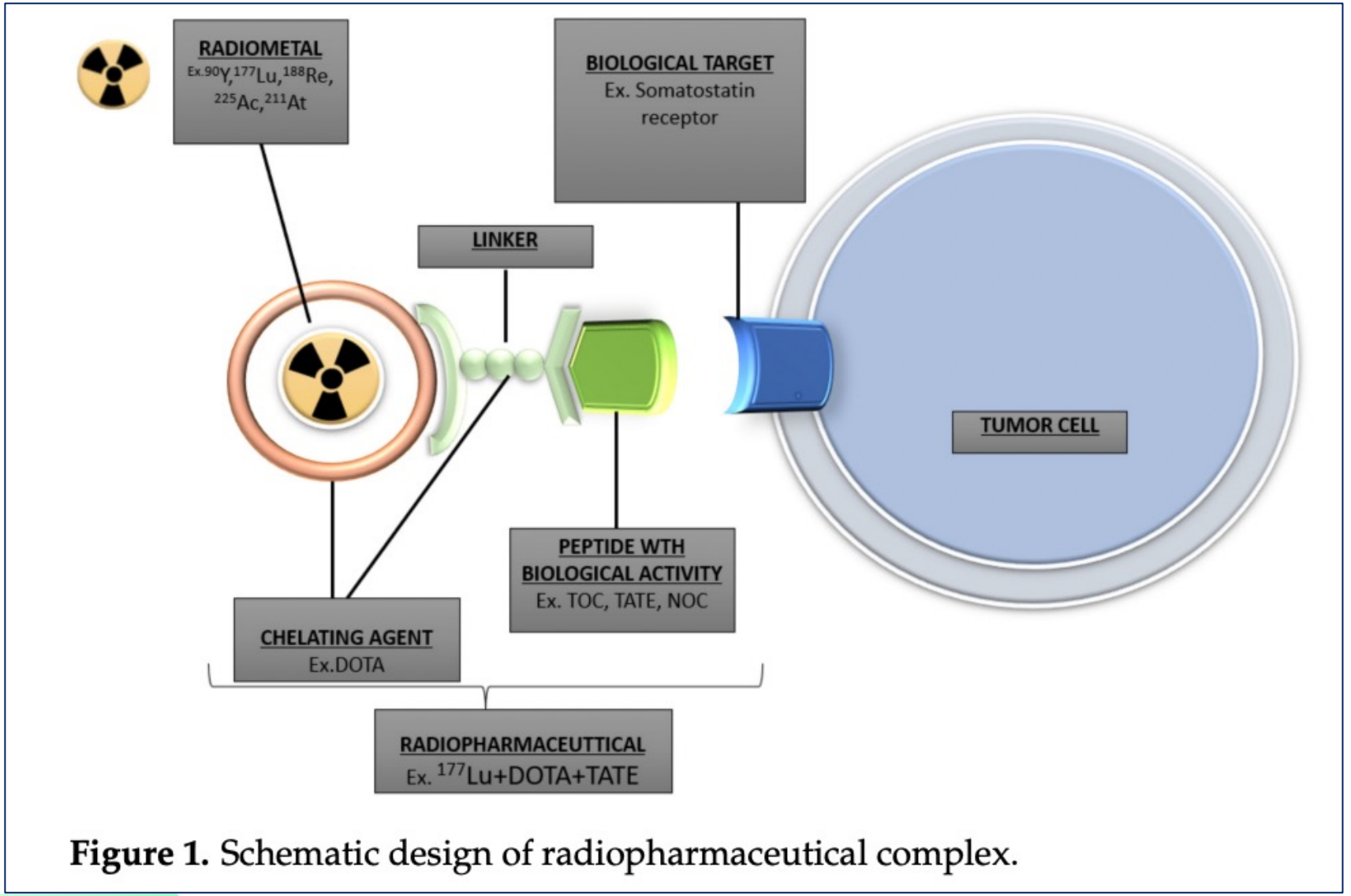


Figure 1. Schematic design of radiopharmaceutical complex.

Olmo-Garcia et al. Cancers (Basel) 2022;14(3):584

Peptide Receptor Radionuclide Therapy – EBTATE™

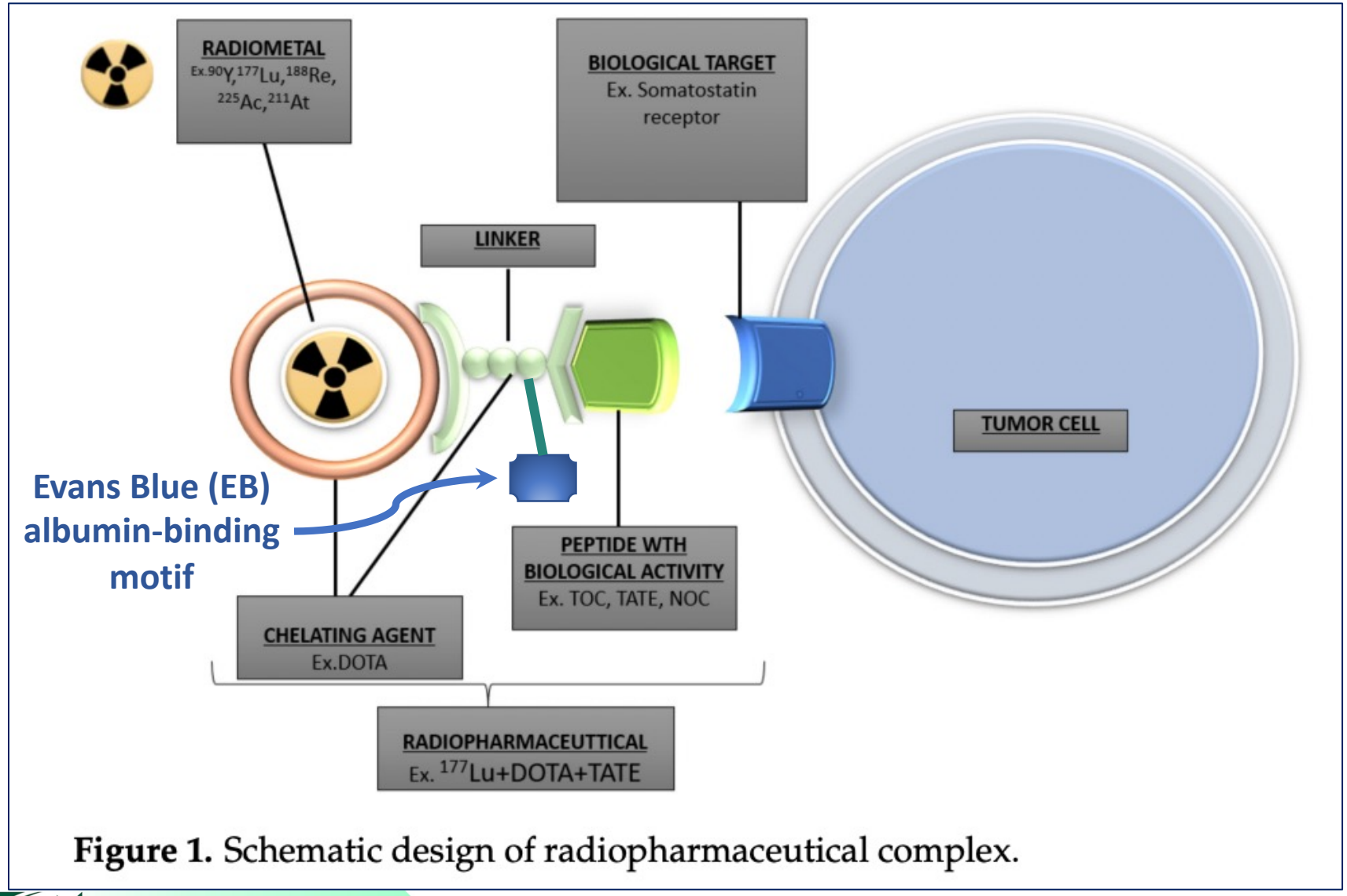


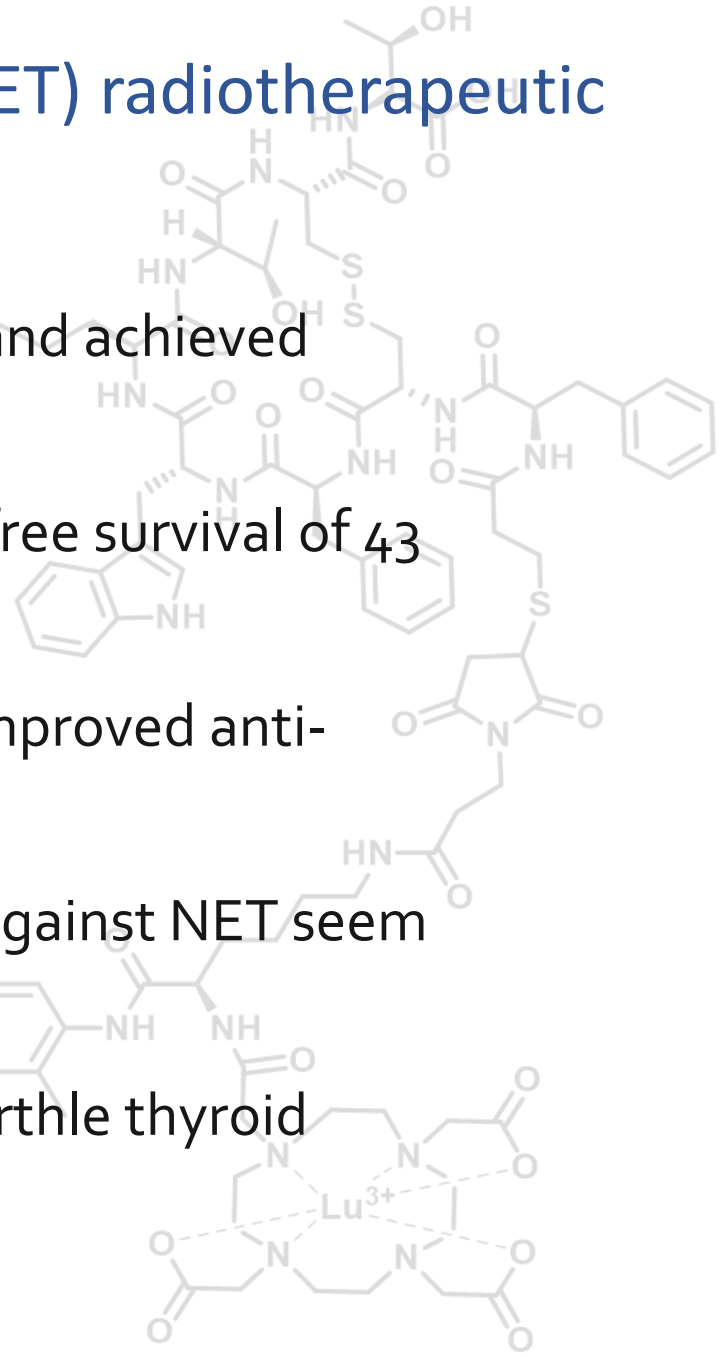
Figure 1. Schematic design of radiopharmaceutical complex.

- EB – Albumin ED_{50} ~2.5 µM
  - Circulatory reservoir
  - Reduced renal
    - Clearance
    - Toxicity
- TATE – SSTR2 ED_{50} ~ 75 nM
- Increased tumor uptake

Adapted from: *Olmo-Garcia et al. Cancers (Basel) 2022;14(3):584*

EBTATE is the next generation neuroendocrine tumor (NET) radiotherapeutic from a new, rationally designed chemical structure

- Early clinical data (N=57 patients) showed that EBTATE is safe and achieved objective responses after a single injection
- 3-year follow-up showed stable NET disease with progression-free survival of 43 months after three cycles of ^{177}Lu-DOTA-EB-TATE
- Head-to-head *in vivo* comparisons of EBTATE in NET showed improved anti-tumor efficacy versus standard of care
- Multiple cycles of escalating doses of EBTATE (N=32 patients) against NET seem to be well tolerated and were effective in tumor control
- EBTATE should also target other SSTR2 expressing tumors (Hürthle thyroid cancer [HTC], nasopharyngeal cancer [NPC],…)



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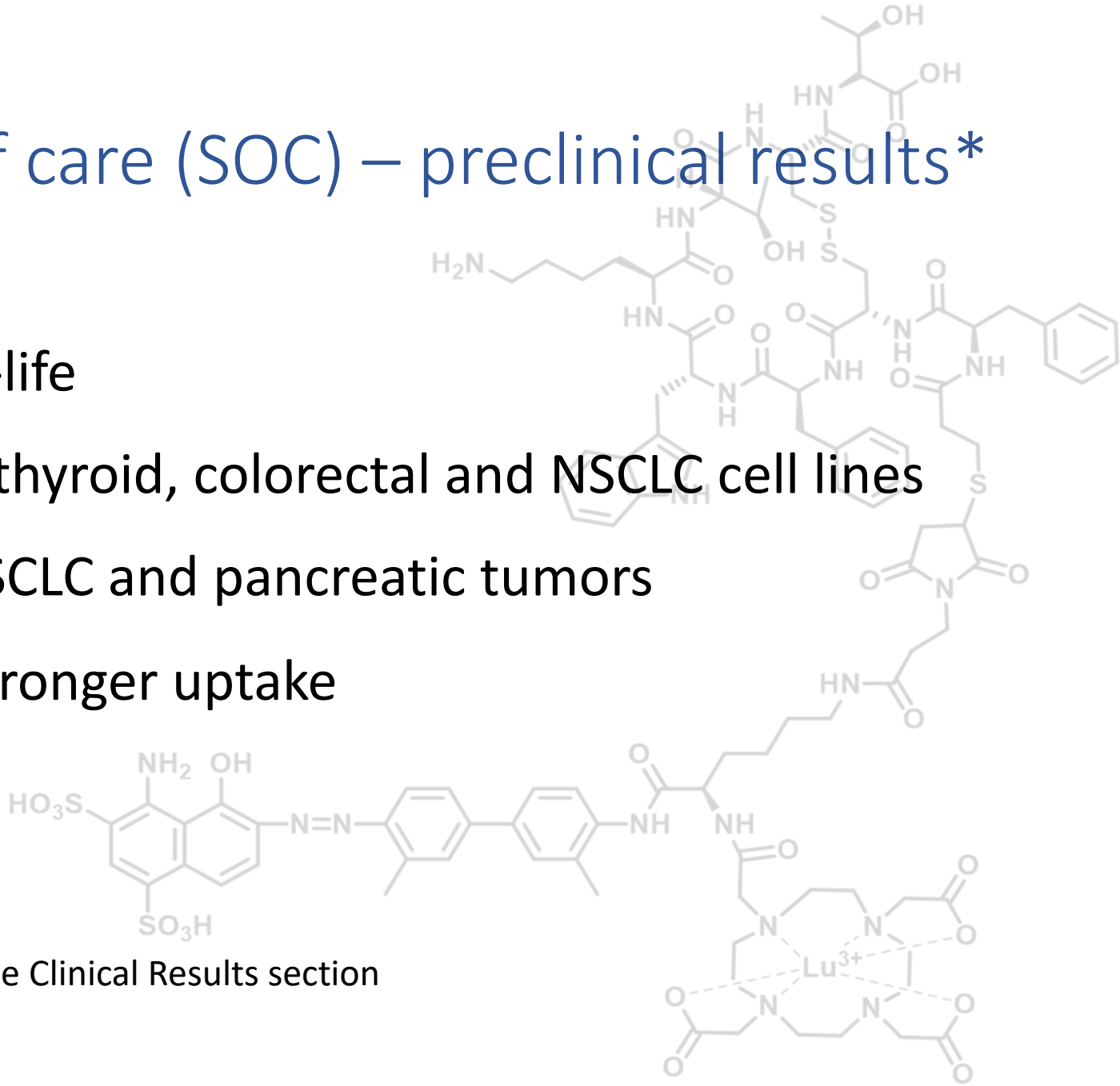
EBTATE™ vs standard of care (SOC) – preclinical results*

- Prolonged circulation half-life
- Stronger tumor uptake in thyroid, colorectal and NSCLC cell lines
- Better tumor control in NSCLC and pancreatic tumors
- Biodistribution parallels stronger uptake
- Comparable safety



*NET medical benefits are described in the Clinical Results section

Better preclinical tumor uptake and treatment response*

Preclinical – xenograft tumor uptake	EBTATE	SOC
Non small cell lung cancer (NSCLC)-% ID/gram	80%	4%
Pancreatic cancer AR42J-standardized uptake value	15.16	3.53
Follicular thyroid (Hürthle cell)-standardized uptake value	4.8	0.28

Preclinical – treatment response	EBTATE	SOC
Non small cell lung cancer (NSCLC)	100% at 18.5 MBq	0% at 18.5 MBq
Pancreatic cancer-AR42J	Protects mice up to 24 days	Mice euthanized in 10 days due to tumor size
Pancreatic cancer –AR32J with Y-90	100% survival to 90 days with at 3.7 & 7.4 Mbq	No survival at 35 days with 7.4 Mbq

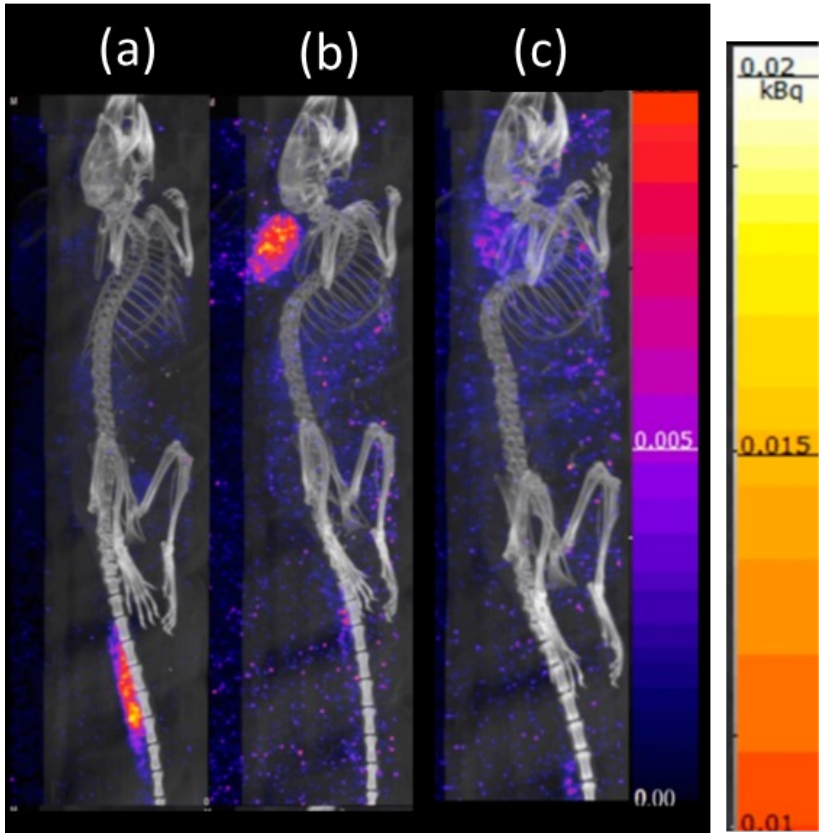
*see the following slides 11 - 15

SUPERIOR TUMOR UPTAKE OF EBTATE -- murine NSCLC model

Results: Uptake of ^{177}Lu–DOTA-EB–TATE

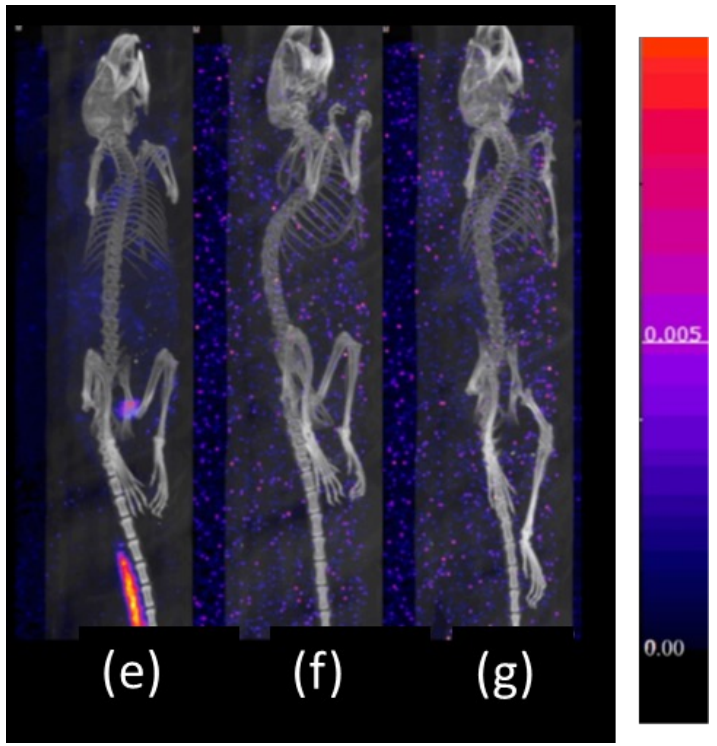
(b) was significantly higher than ^{177}Lu–DOTA–TATE (f) in the tumor.

Uptake at the target was blocked as shown in (c).



(a & b) ^{177}Lu–DOTA-EB–TATE without blocking at 1 and 24 h post injection and (c) with blocking (125 µg of DOTA-EB–TATE co-injected with the dose) at 24 h pi.

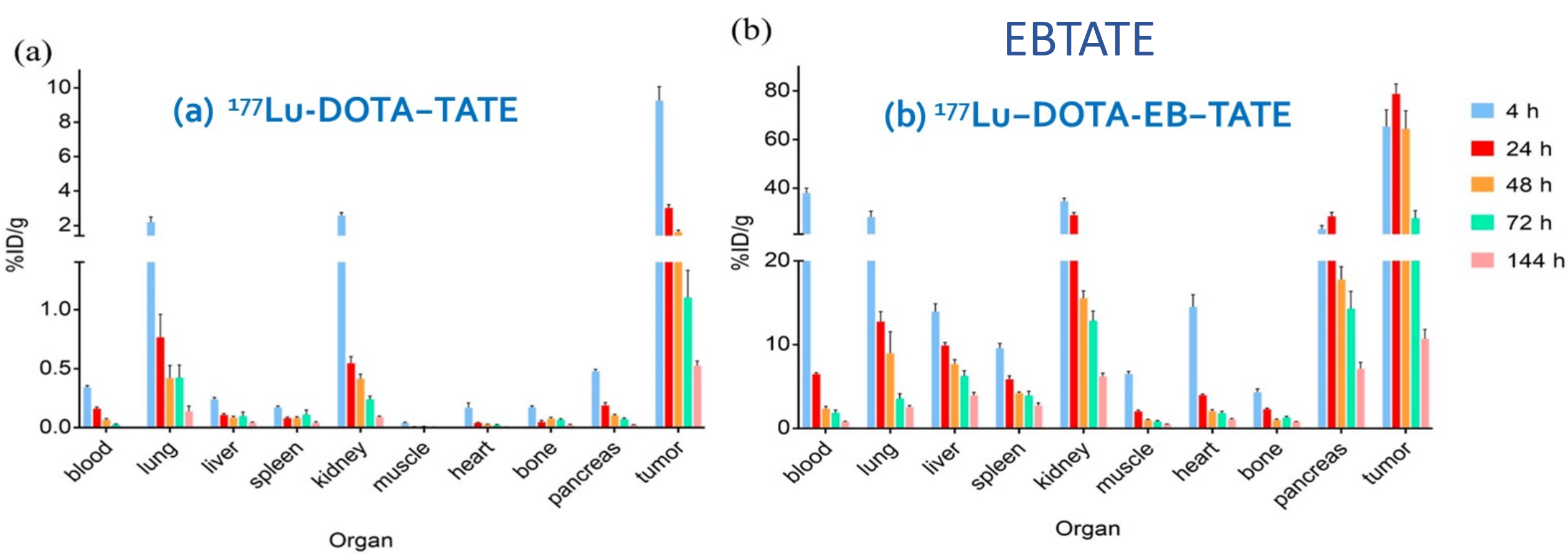
(e & f) ^{177}Lu–DOTA–TATE without blocking at 1 and 24 h post injection and (g) with blocking (125 µg of DOTA–TATE) at 24 h pi.



Bandara et al. Bioconjugate Chem 2018; 29(7): 2448-2454

A low dose of EBTATE will clear slowly and stay in the tumor longer

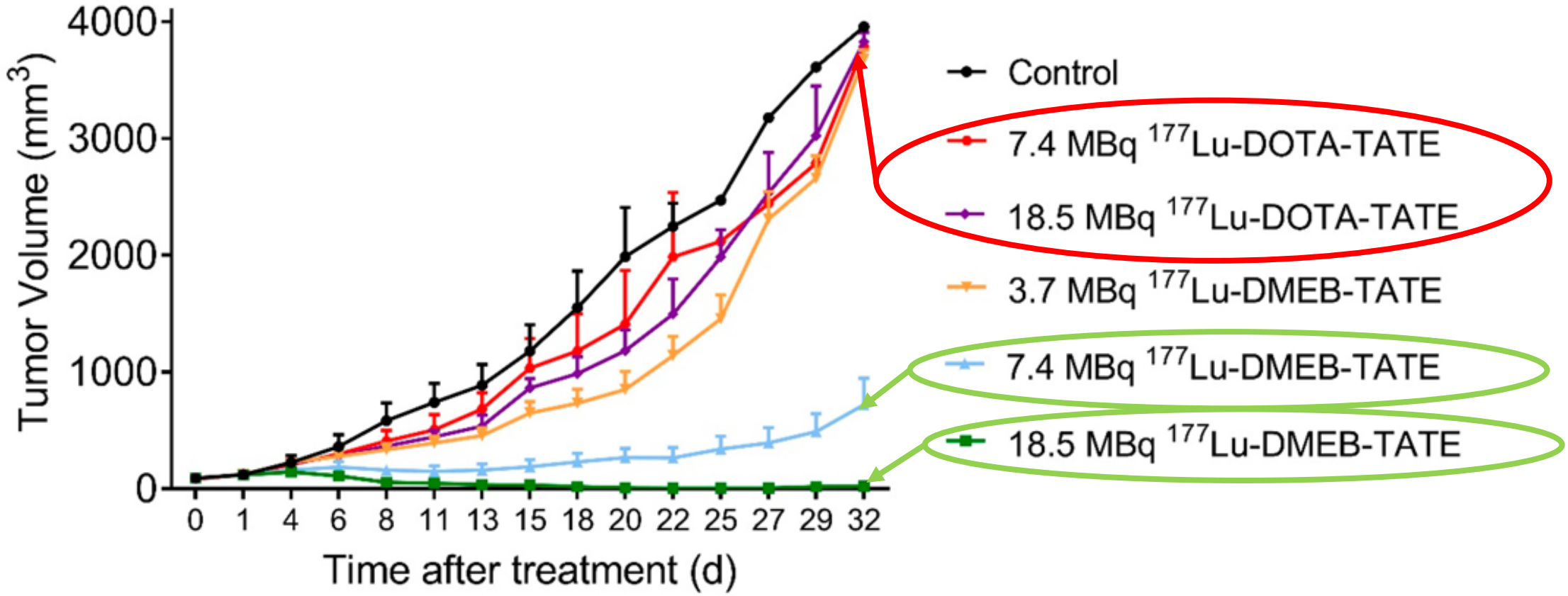
In vivo biodistribution studies in A427-7 (NSCLC) bearing mice



Bandara et al. Bioconjugate Chem 2018; 29(7): 2448-2454

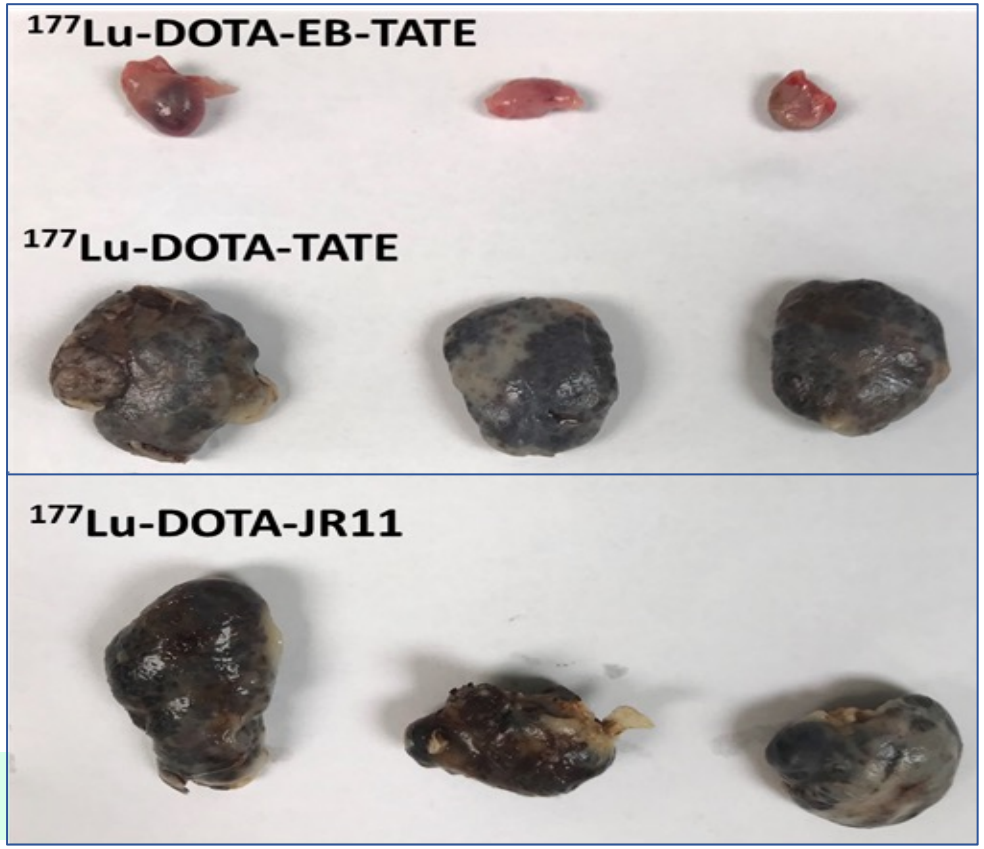
EBTATE shrinks NSCLC tumors, SOC does not

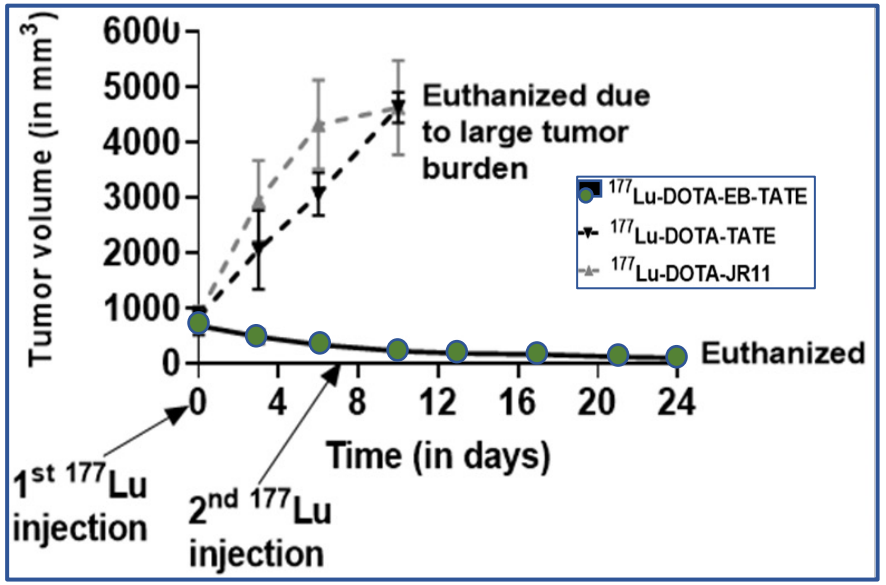
^{177}Lu-DOTA-EB-TATE (^{177}Lu-DMEB-TATE) tumor therapy: tumor growth in athymic nude mice with A427-7 xenografts
Bandara et al. Bioconjugate Chem 2018; 29(7): 2448-2454

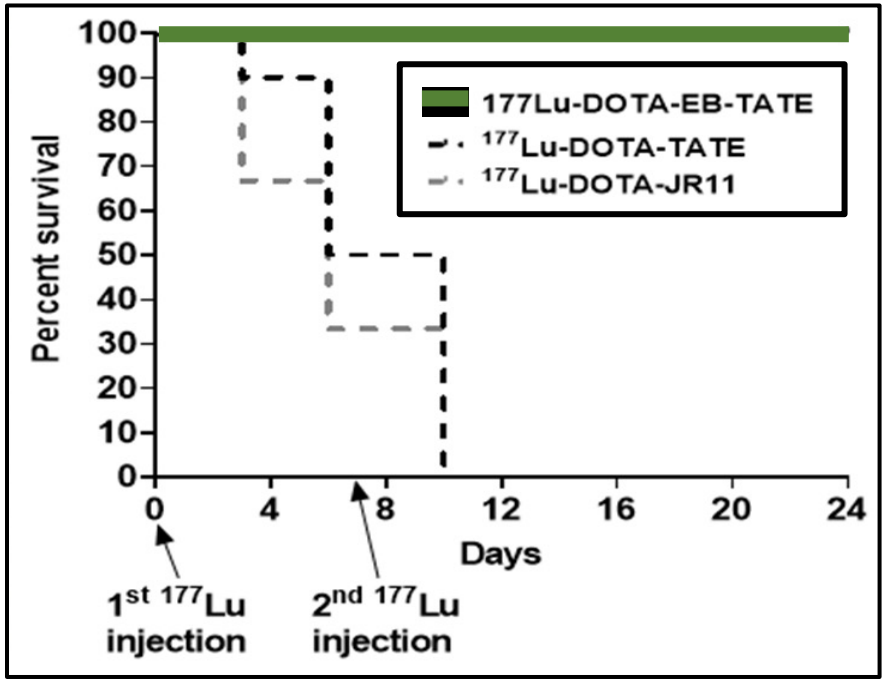


Pancreatic cancer tumors responded to EBTATE, those treated with ^{177}Lu-DOTA-TATE did not

PRECLINICAL EFFICACY OF EBTATE vs. ^{177}Lu-DOTA-TATE in Pancreatic cancer AR42J MOUSE Model *Thakur et al. Clin Cancer Res 2021; 27(5): 1399-1409*

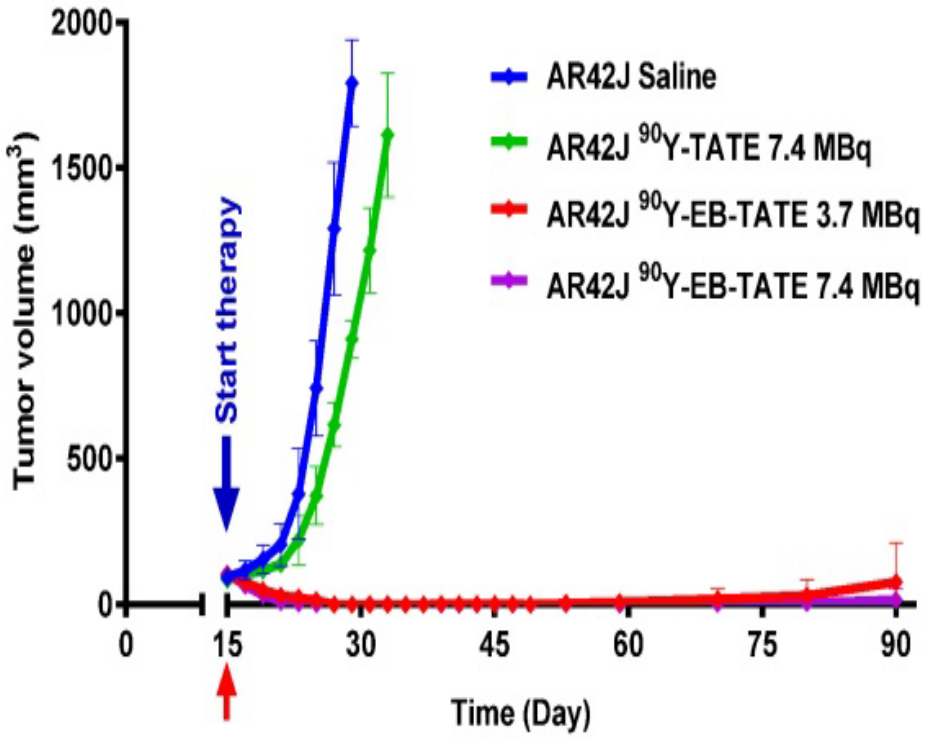


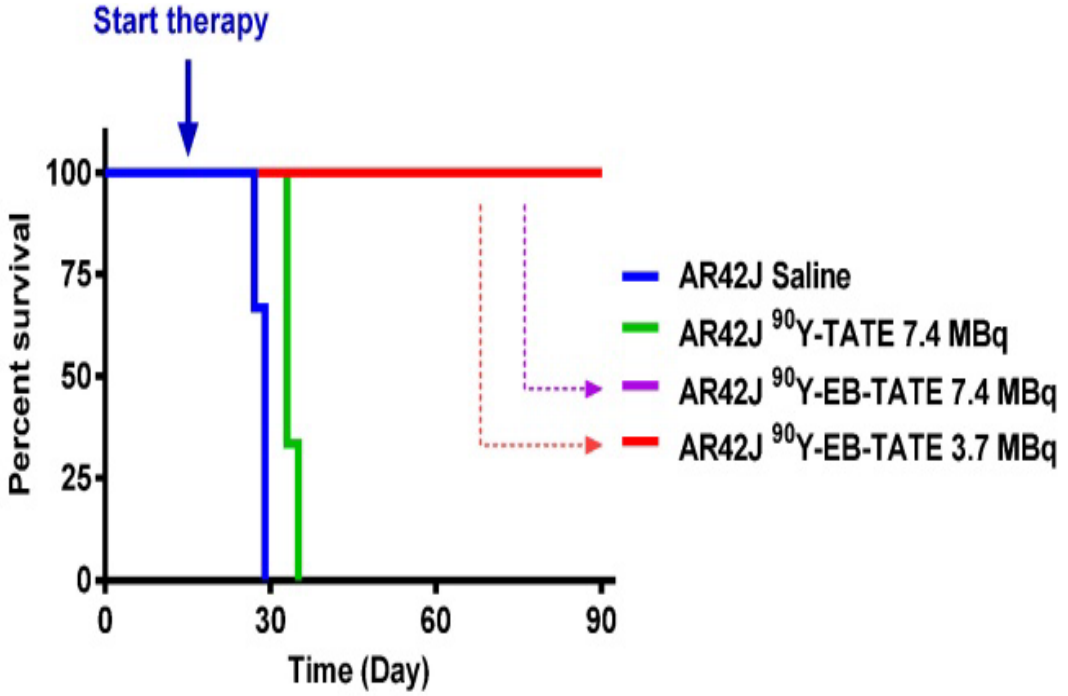




Pancreatic tumor volume and survival of mice injected with ^{90}Y-TATE or ^{90}Y-EB-TATE show superior effect with EB

Tian et al. Theranostics 2018; 8:735-745





Clinical Comparison: EBTATE vs SOC

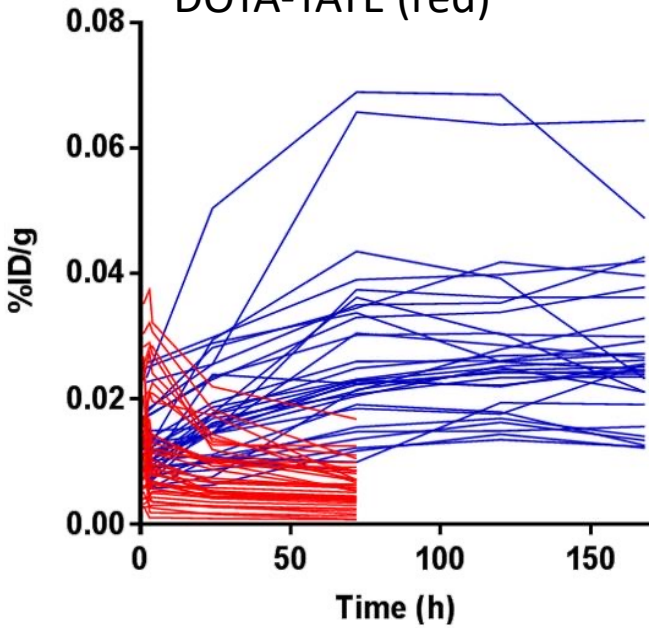
Safety, Pharmacokinetics, and Dosimetry of a Long-Acting Radiolabeled Somatostatin Analog ^{177}Lu-DOTA-EB-TATE in Patients with Advanced Metastatic Neuroendocrine Tumors

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

EBTATE™ reached peak slower, and had a prolonged plateau compared to ^{177}Lu-DOTA-TATE (TATE)

A

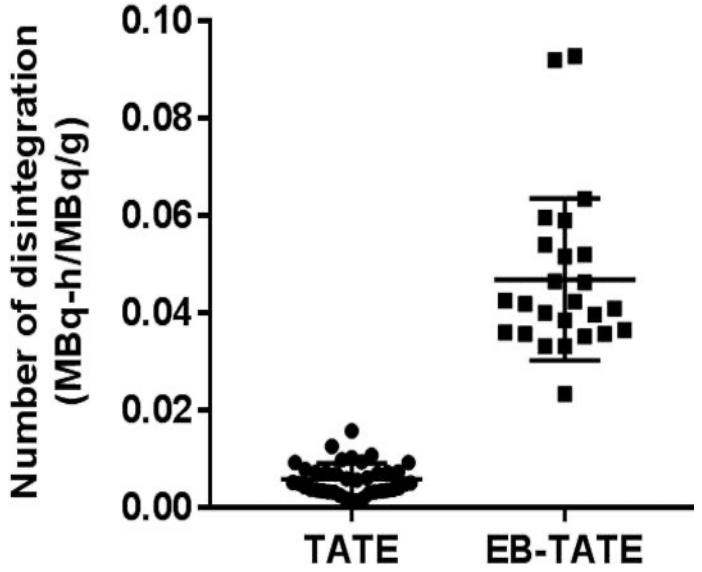
Time Activity
After EBTATE™(blue) & DOTA-TATE (red)



EBTATE™ showed 7.9-fold increase of lesion radiation counts vs TATE

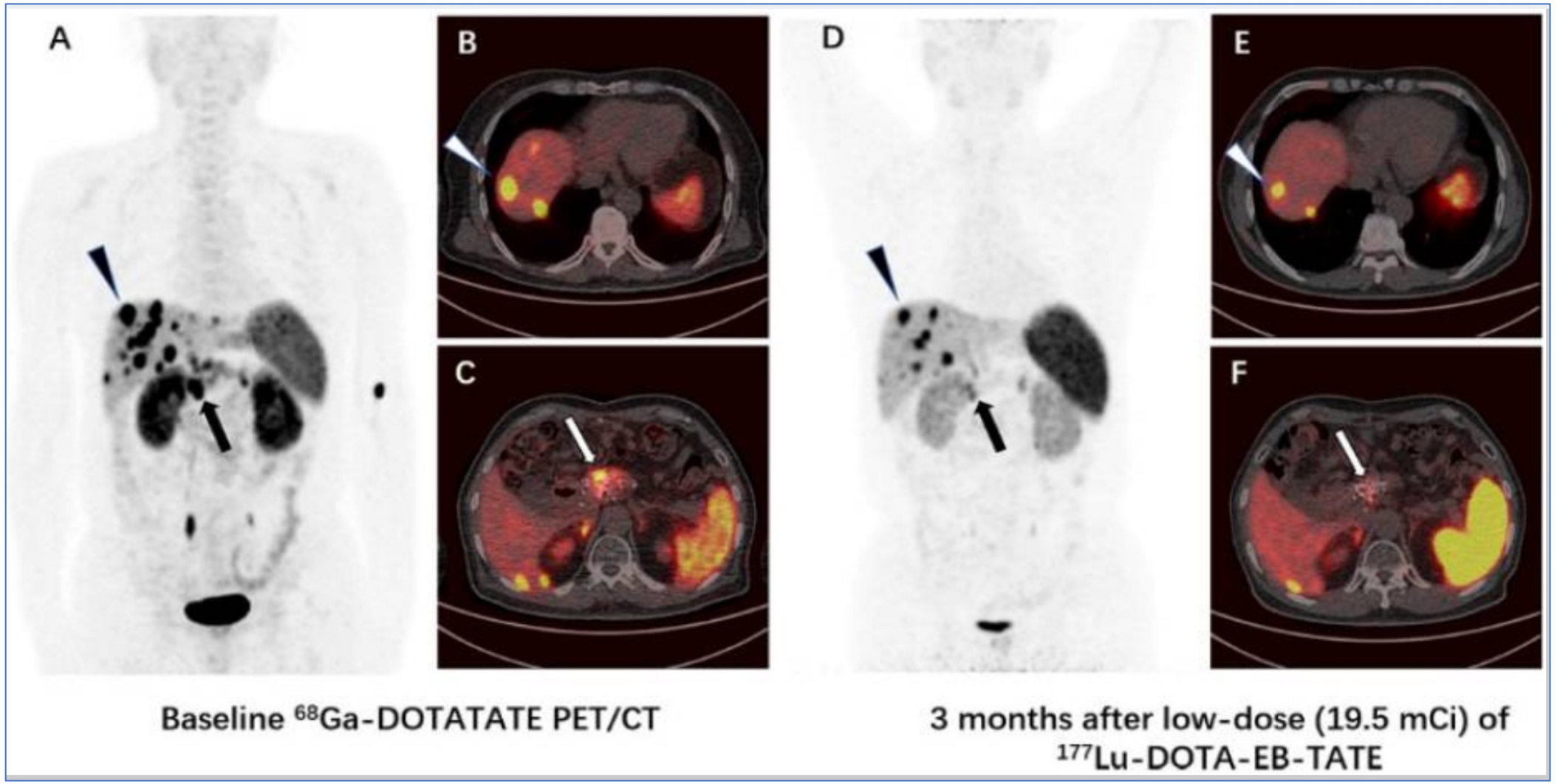
B

# of Disintegrations of ^{177}Lu



Tumor size reduction in patients after a single injection of EBTATE™

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



PET/CT response (EORTC criteria)-^{68}Ga-DOTATATE

Liu et al. J Nucl Med 2021; 62(3): 386-392

Efficacy	Group A (1.17 GBq) N=12	Group B (1.89 GBq) N=6	Group C (3.97 GBq) N=14
CR (%)	0	0	0
PR (%)	50	50	42.9
SD (%)	16.7	33.3	28.6
PD (%)	33.3	16.7	28.6
DRR (%)	50	50	42.9
DCR (%)	66.7	83.3	71.5

Patients seemed to tolerate ^{177}Lu-DOTA-EB-TATE well, even up to 3.97 GBq/cycle. The overall disease control rate, as well as the percentage decrease in tumor SUVmax, were highest with a 1.89 GBq dose, followed by 3.97 and 1.17 GBq.

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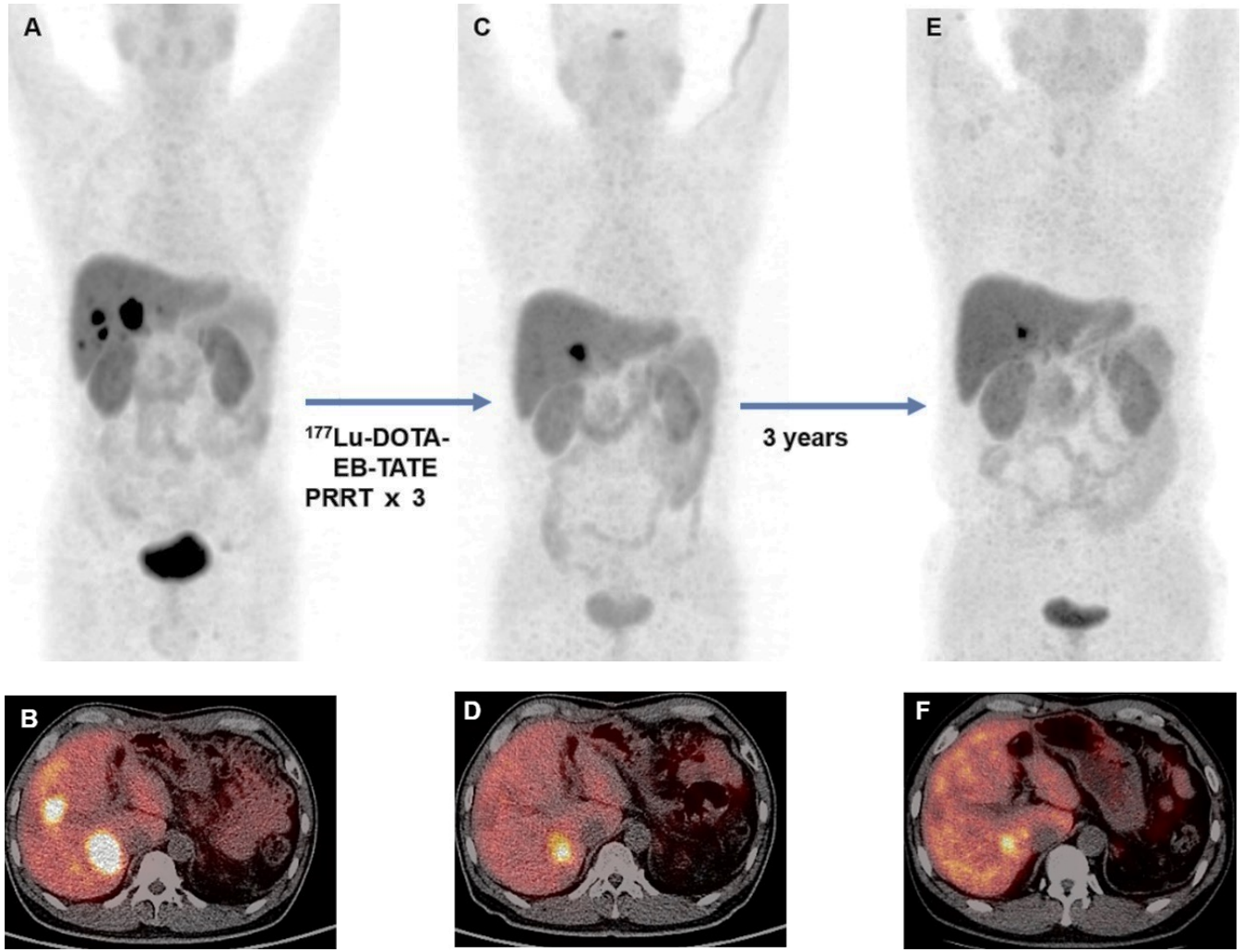
3-year follow up: Patient treated with ^{177}Lu-DOTA-EB-TATE (3 cycles) with cumulative administered activity of 12.4 GBq

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



^{68}Ga-DOTA-TATE PET/CT diagnostic tracking at 3-year follow-up showed stable disease (E, MIP image; F, fused PET/CT) with progression-free survival of 43 months from the first cycle of ^{177}Lu-DOTA-EB-TATE PRRT

Progression-free survival (PFS)

EBTATE (3 cycles) is as effective as ^{177}Lu-DOTA-TATE (4 cycles) (3-year study)

DRUG	PATIENTS	DOSE (GBq)	Cycles	PFS	Authors
EBTATE	29	3.7	3	36*	Jiang et. al.
SOC	74	7.4	4	26	Ezzidin et. al.
SOC	443	7.4	4	29	Barbander et. al.
SOC	104	7.4	4	37	Kennedy et. al.
SOC	Multiple studies	7.4	4	26-37	Others, Kwekkeboom, Sabet, Paganelli et. al.

* after a median follow-up of 46 months. *Jiang et al. Theranostics 2022; 12(5): 6437-6445*

EBTATE Safety: Low, long-term hematotoxicity, nephrotoxicity and hepatotoxicity (CTCAE 5.0) among 29 patients similar to SOC*

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

Toxicity	Grade 1 (# of patients)	Grade 2 (# of patients)	Grade 3 (# of patients)	Grade 4 (# of patients)
Leukopenia	1	3	0	0
Thrombocytopenia	1	0	1	0
Anemia	1	2	0	0
Nephrotoxicity	0	0	0	0
Hepatoxicity	1	0	0	0

**Danthala et al. 177Lu-DOTA-TATE therapy in patients with neuroendocrine tumors: 5 years' experience from a tertiary cancer care centre in India. Eur J Nucl Med 2014; 41: 1319-1326*

EBTATE™ Competitive Environment

Lutathera® is the current Standard of Care (SOC)

EBTATE® shows strong partial response at lower dose than all other reported products

Sponsor	Drug	Status	Dose (mCi)	Partial response	Radio-nuclide
Generic (~20)	Octreotide	Commercial	N/A	4%	N/A
Novartis	Lutathera	Launched	200	19%	Lu-177
ITM	Lu-177-Edotreotide	Phase III	200	54%	Lu-177
MTTI	EBTATE	Phase I/II	50	50%	Lu-177
Point	PNT 2004	Phase I			Lu-177
Radiomedix / Orano Med	AlphaMed	Phase II			PB-212
Rayze Bio	RYZ101	Phase Ib/II			Ac-225
ViewPoint	VMT-a-NET	Phase I			Pb-203

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Differentiating EBTATE as an anticancer agent

- EBTATE is the next generation of NET drugs, supported by strong IP and efficacy
- Value is tied to product performance and safety vs other anticancer agents, not whether it is a targeted drug or the choice of isotope
- EB imparts unique benefits to any targeting peptide
- MTTI owns IP that includes ^{225}Ac and other radionuclides to 2037
- Real World Evidence from our China studies in 57 patients (which supported our IND – February 2021) and ongoing US and Asian trials position us well for Phase II & III trials

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EBTATE™ (^{177}Lu-DOTA-EB-TATE) Conclusions

- 3-year follow-up showed stable disease with progression-free survival of 43 months after three cycles of ^{177}Lu-DOTA-EB-TATE (N=30 patients)
- In a head-to-head *in vivo* comparison, EBTATE showed improved anti-tumor efficacy versus DOTA-TATE
- Early clinical data showed that EBTATE is safe and achieved objective responses after a single injection
- Multiple cycles of escalating doses of EBTATE (N=32 patients) seem to be well tolerated and were effective in tumor control
- EBTATE should also target Hürthle cell thyroid cancer and nasopharyngeal cancer

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MTTI's radiotherapeutic/radiodiagnostic platform

EBRGD™ (^{177}Lu-DOTA-EB-RGD)

Targeted peptide radiotherapeutic platform for $\alpha_v\beta_3$ expressing tumors

Peptide Receptor Radionuclide Therapy – EBRGD™

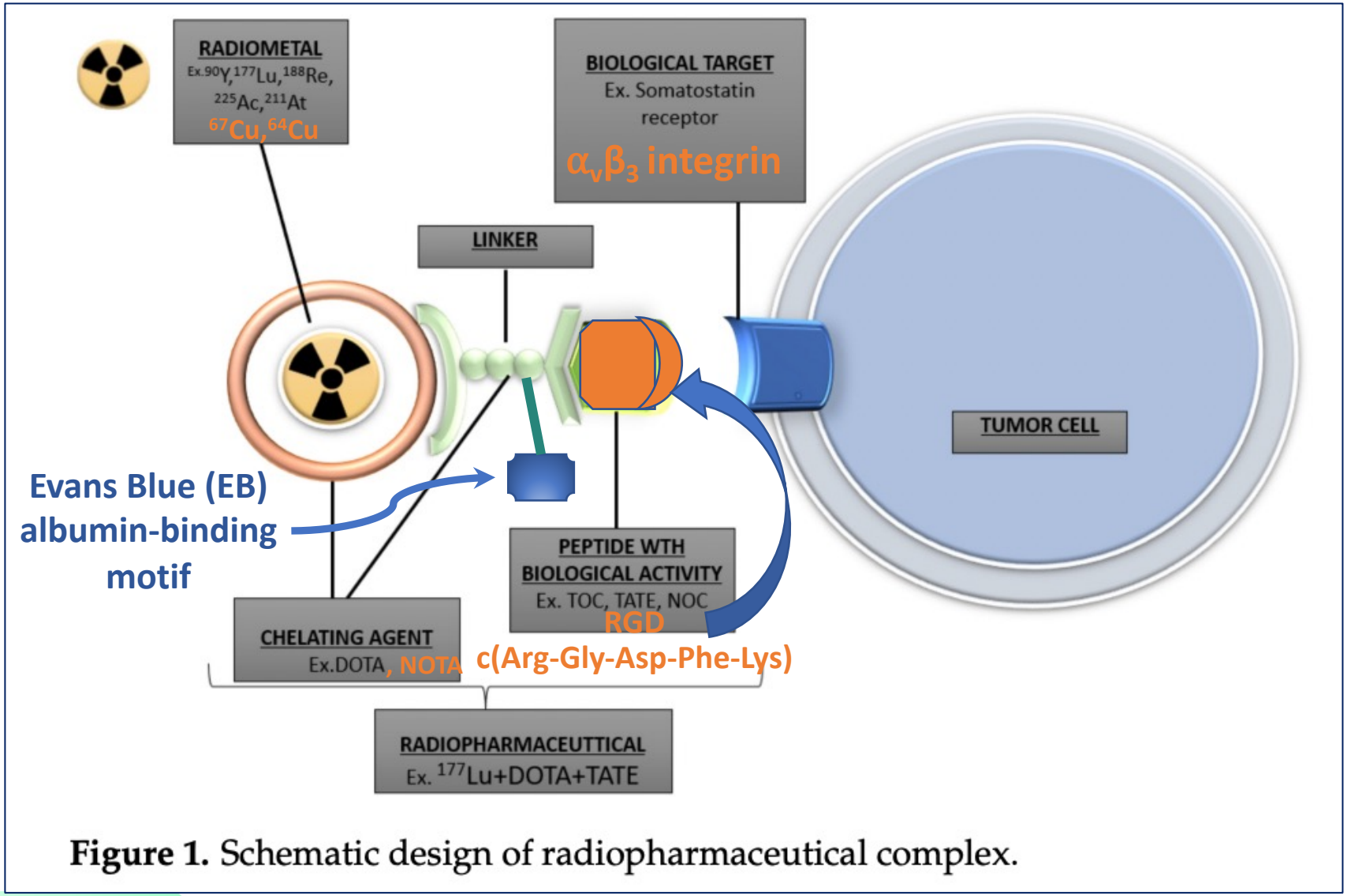
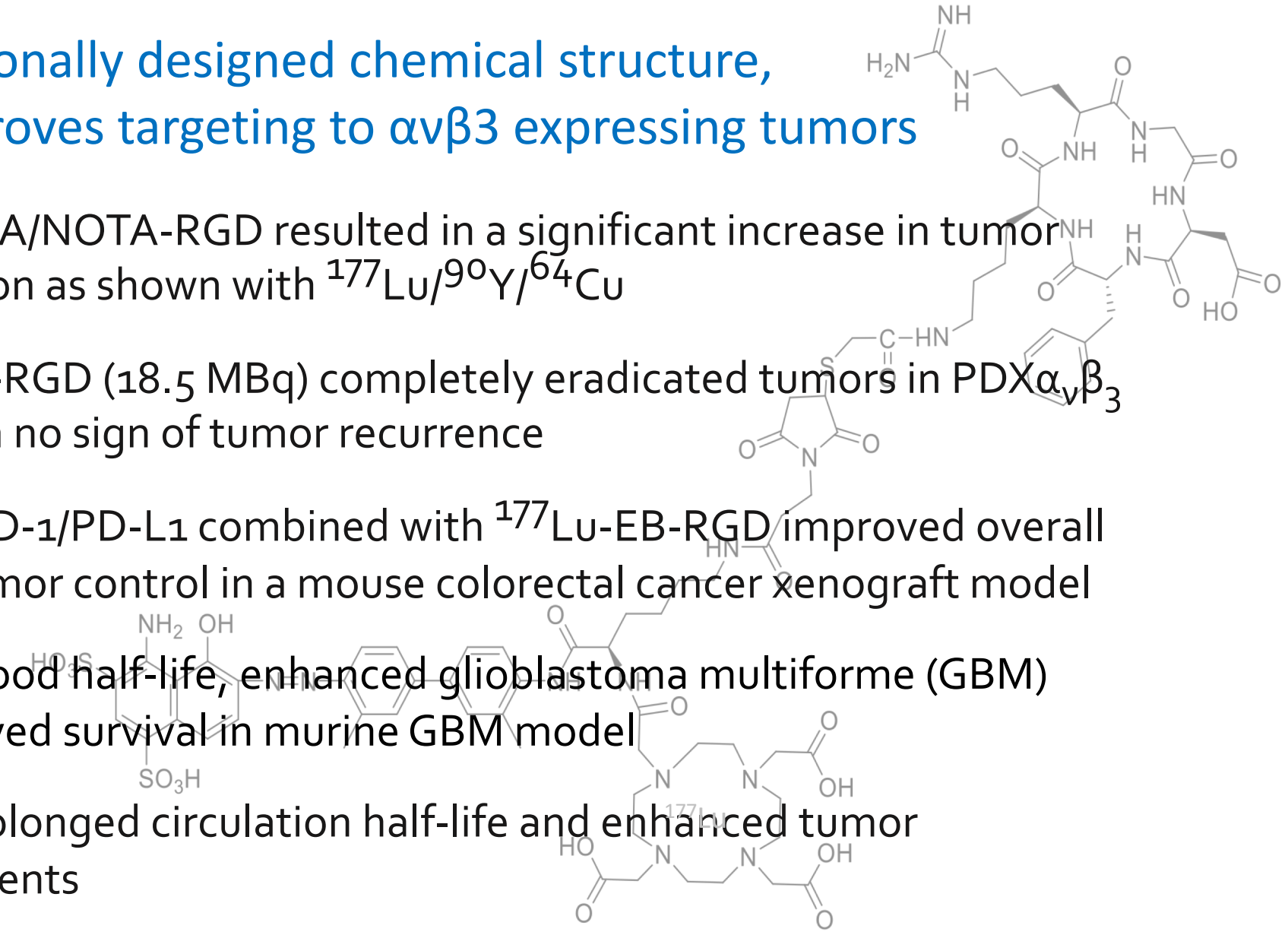


Figure 1. Schematic design of radiopharmaceutical complex.

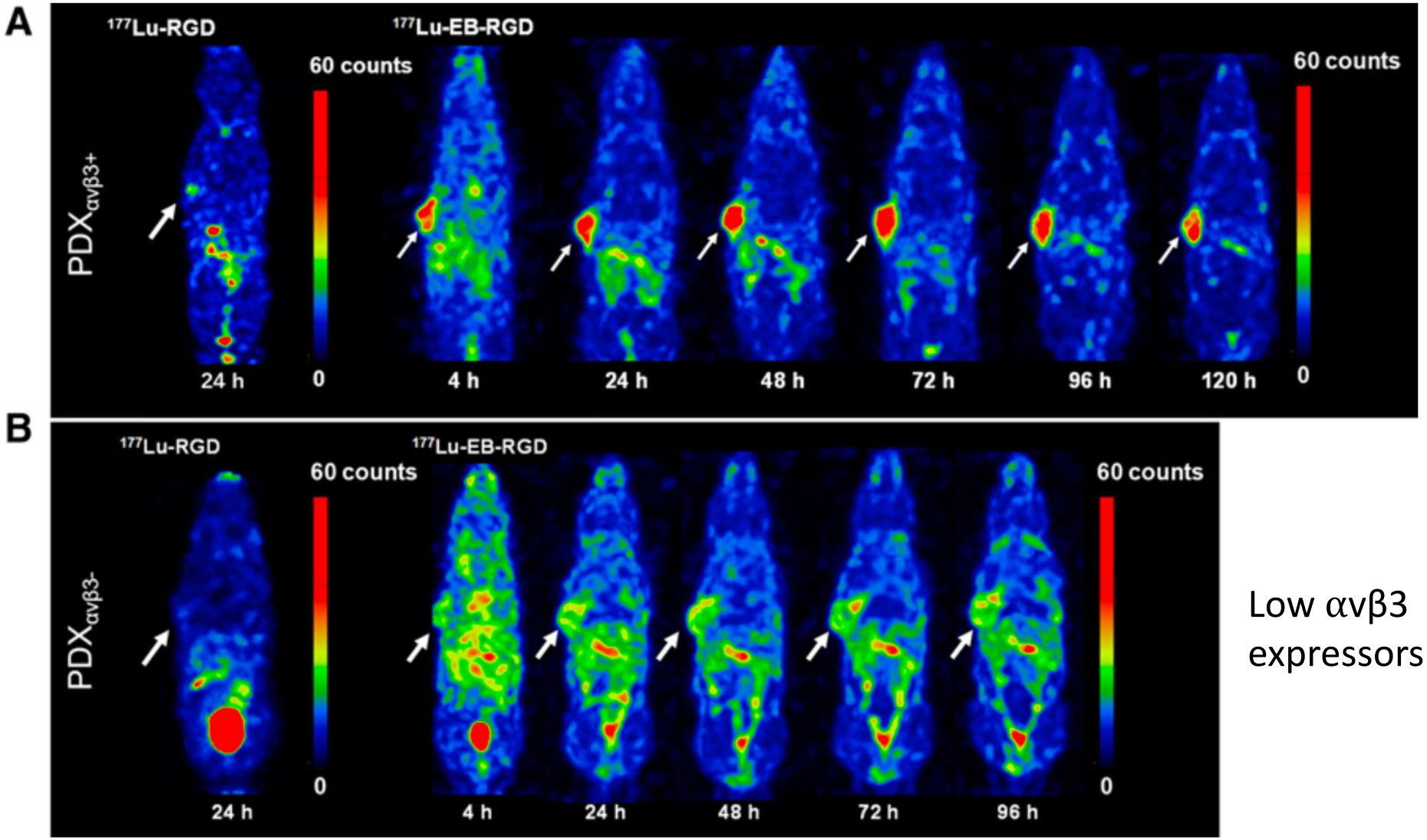
Adapted from: *Olmo-Garcia et al. Cancers (Basel) 2022; 14(3): 584*

EBRGD, from the new, rationally designed chemical structure, prolongs half-life and improves targeting to αvβ3 expressing tumors



- Conjugation of EB to DOTA/NOTA-RGD resulted in a significant increase in tumor uptake and tumor retention as shown with $^{177}Lu/^{90}Y/^{64}Cu$
- A single dose of ^{177}Lu-EB-RGD (18.5 MBq) completely eradicated tumors in PDX$\alpha_v\beta_3$ NSCLC mouse model with no sign of tumor recurrence
- Concurrent blockade of PD-1/PD-L1 combined with ^{177}Lu-EB-RGD improved overall survival and long-term tumor control in a mouse colorectal cancer xenograft model
- ^{90}Y-EB-RGD increased blood half-life, enhanced glioblastoma multiforme (GBM) tumor uptake, and improved survival in murine GBM model
- ^{64}Cu-EB-RGD showed prolonged circulation half-life and enhanced tumor accumulation in GBM patients

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



High αvβ3 expressors

Low αvβ3 expressors

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

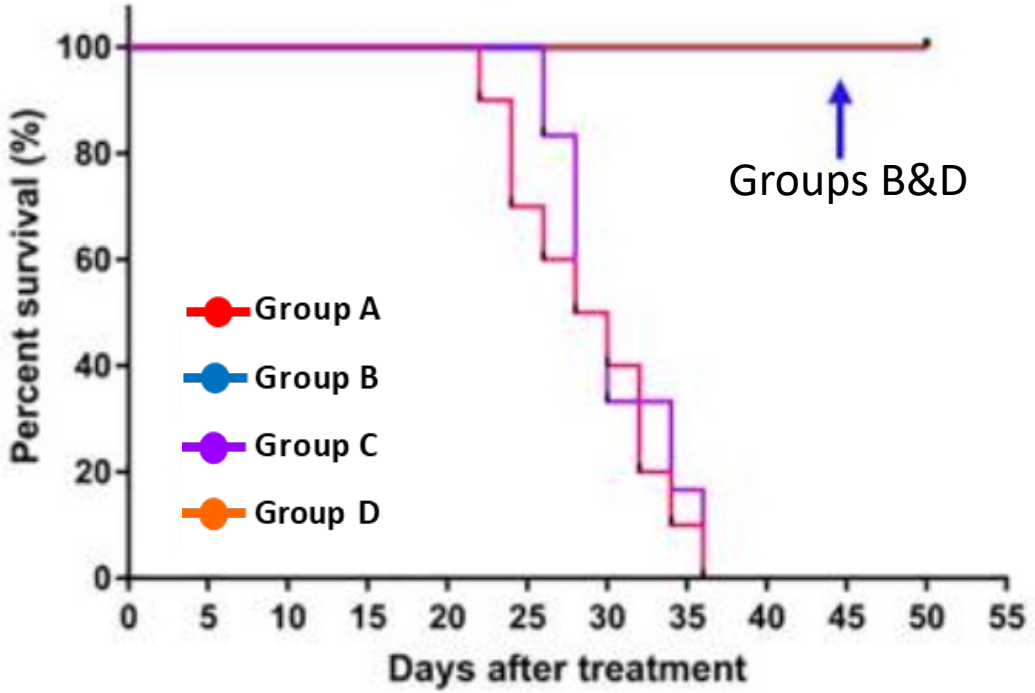
Tumor volume regression and improved survival of αvβ3+ PDX (NSCLC) mice treated with ^{177}Lu-EB-RGD

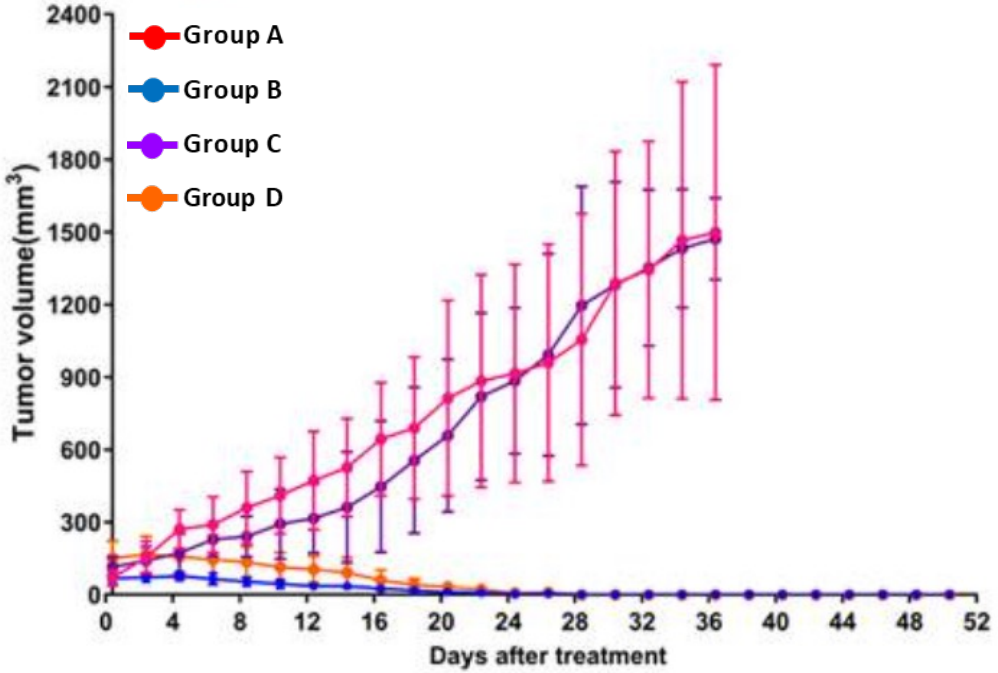
Day 0 — Group A: Saline

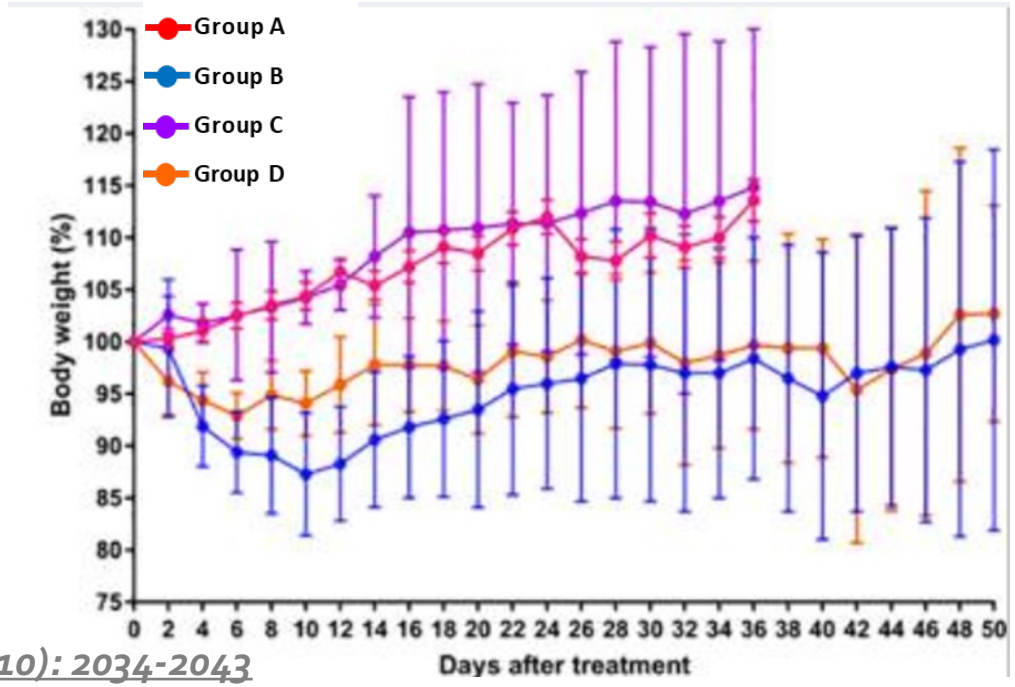
Day 0 — Group B: ^{177}Lu-EB-RGD (18.5 MBq)

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

Day 0 — Group D: ^{177}Lu-EB-RGD (29.6 MBq)

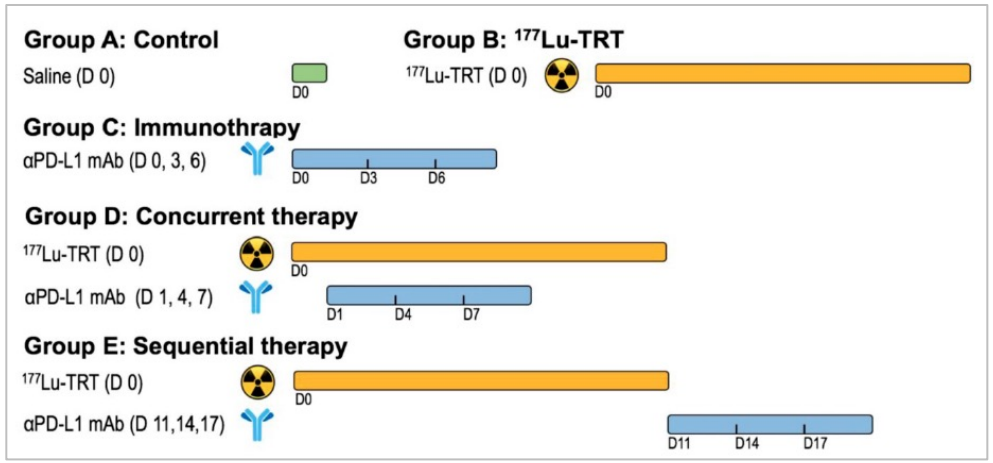


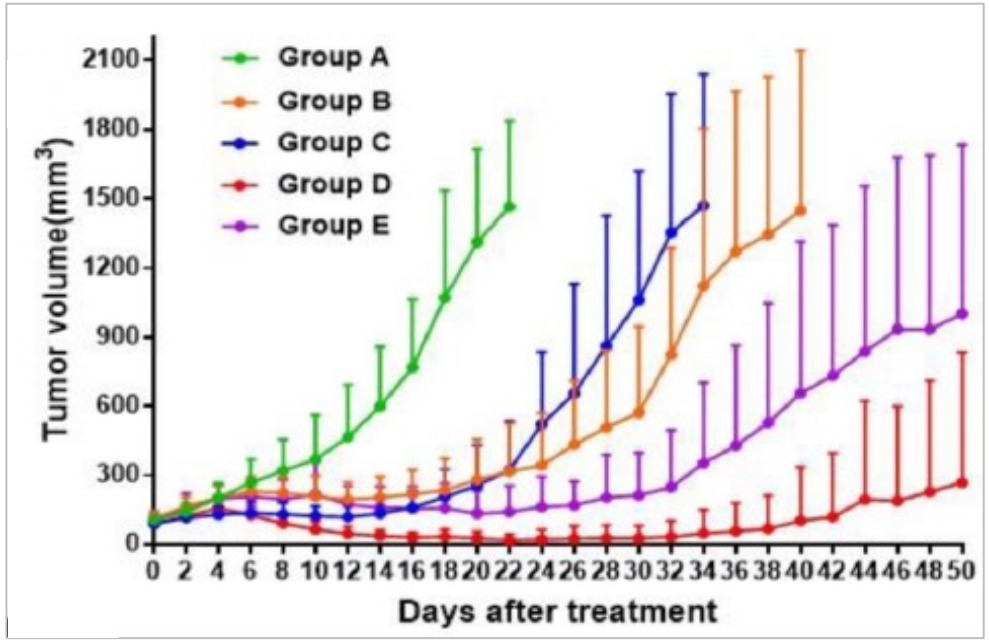


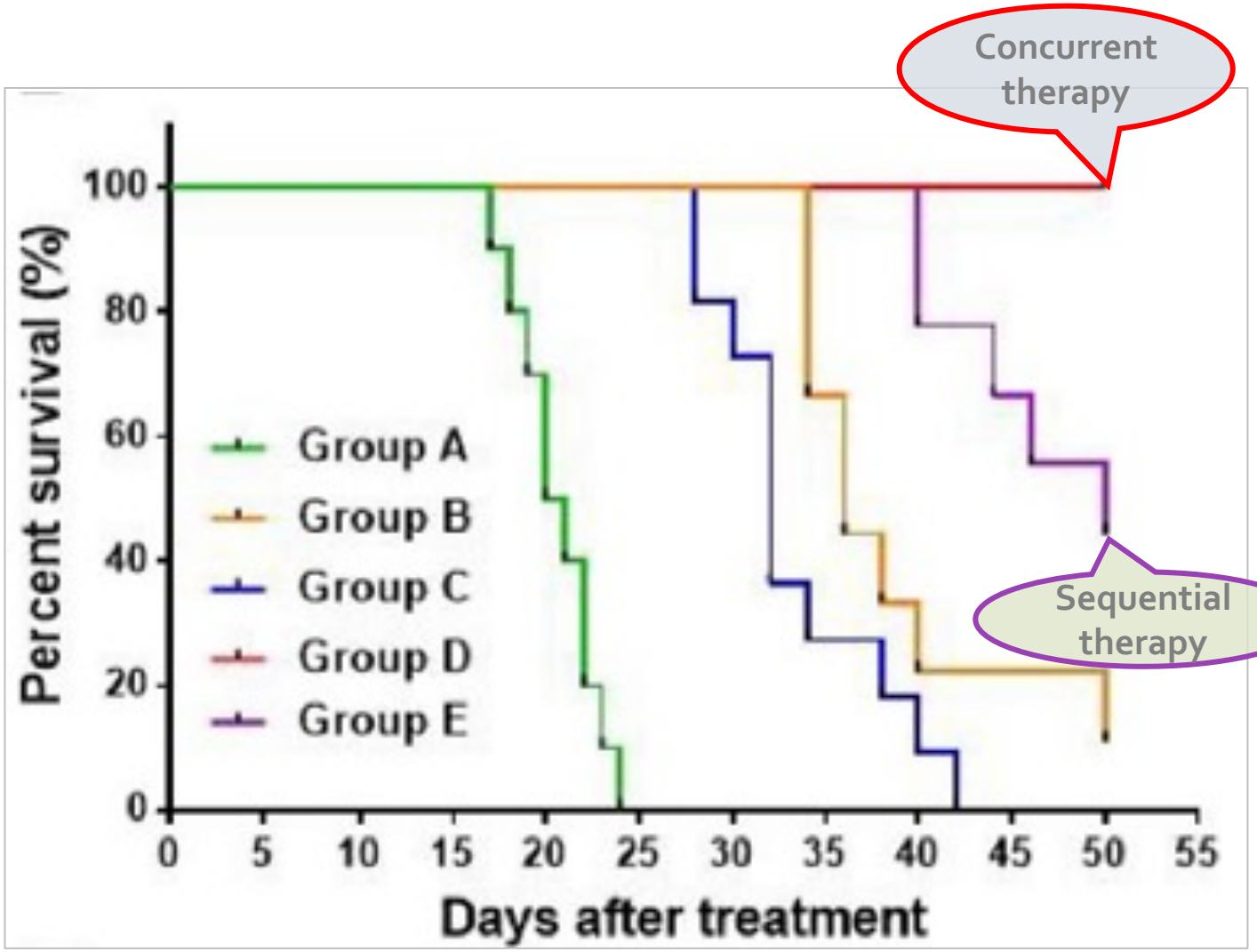


Zhao et al. Mol Cancer Ther 2020; 19(10): 2034-2043

EBRGD enhances immunotherapy efficacy in colorectal cancer



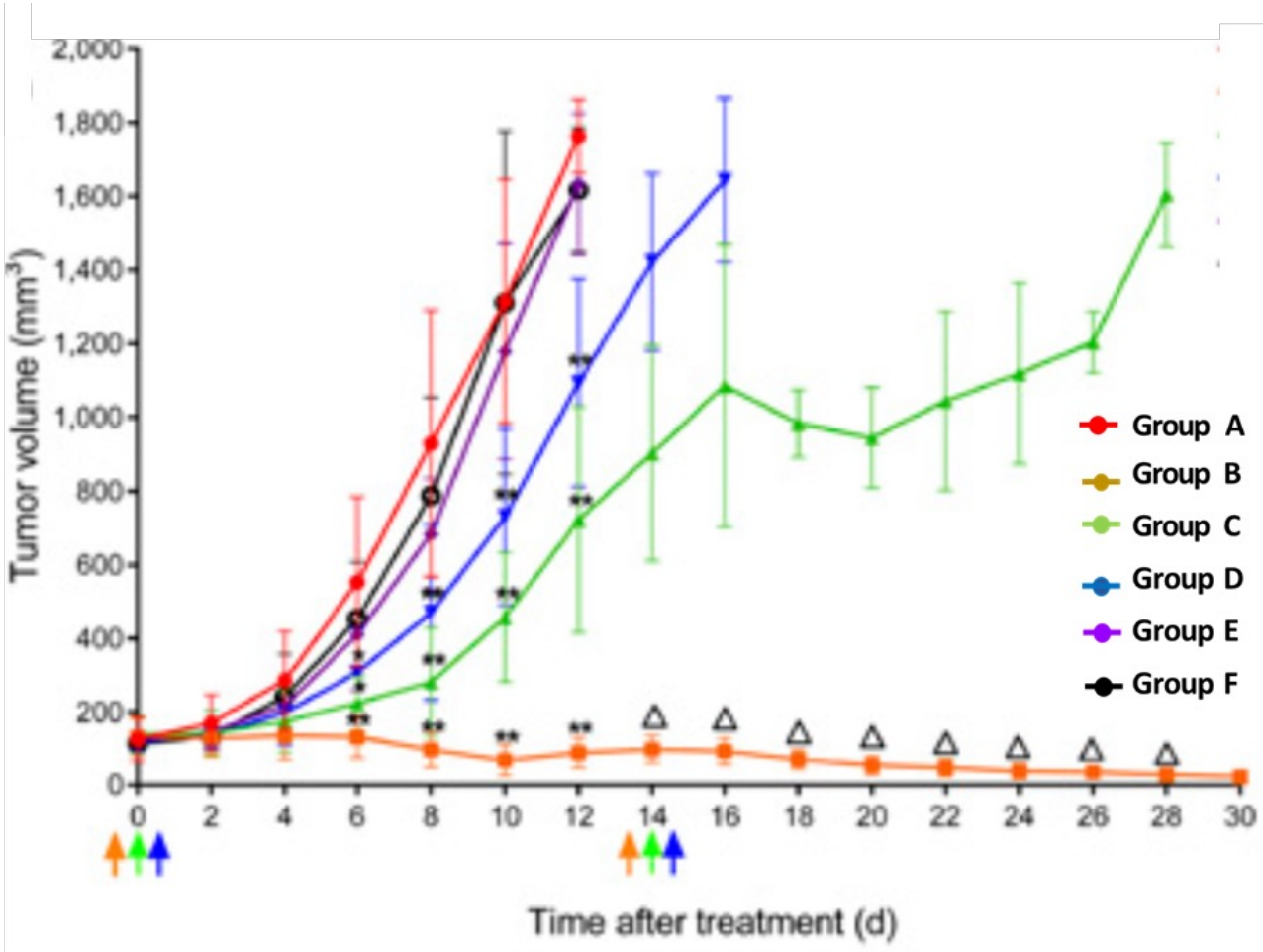


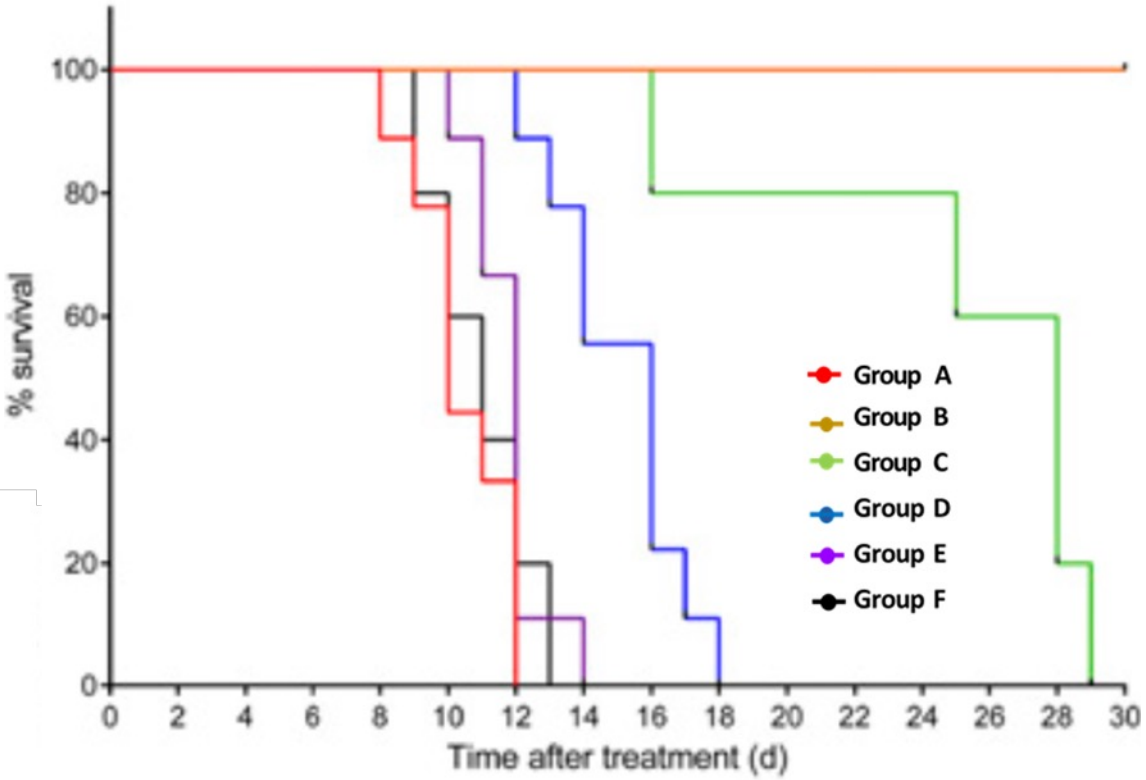


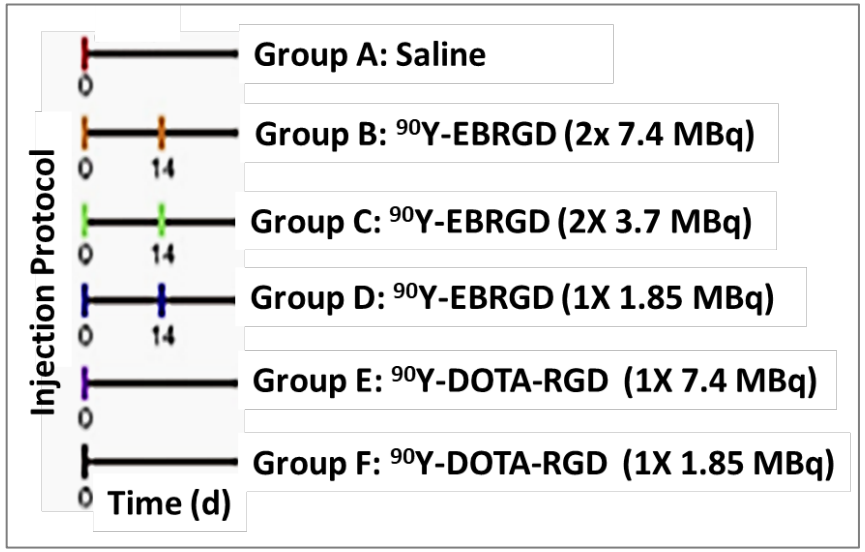
Chen et al. Theranostics 2019; 9(25): 7948-7960

GBM tumor volume regression, improved survival of mice injected with increasing dose of ^{90}Y-EB-RGD and complete eradication of tumor at high dose

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



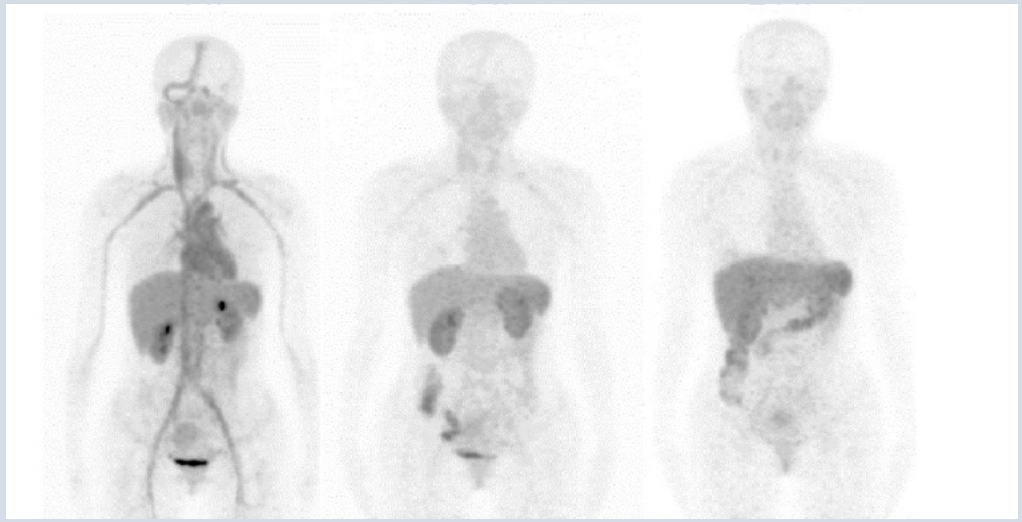




^{64}Cu-EBRGD (Glioblastoma targeting & potential therapy)

Healthy human volunteers

Three healthy volunteers (2 males and 1 female) underwent whole-body PET acquisitions at 1, 8 and 24 h time points after bolus injection of ^{64}Cu-EB-RGD (101.1±9.3, 92.5 -111 MBq).

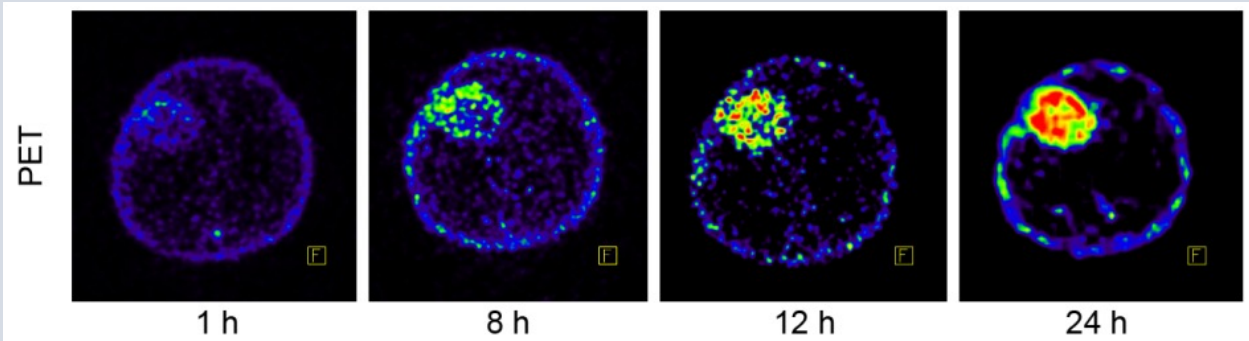


1h 8h 24h

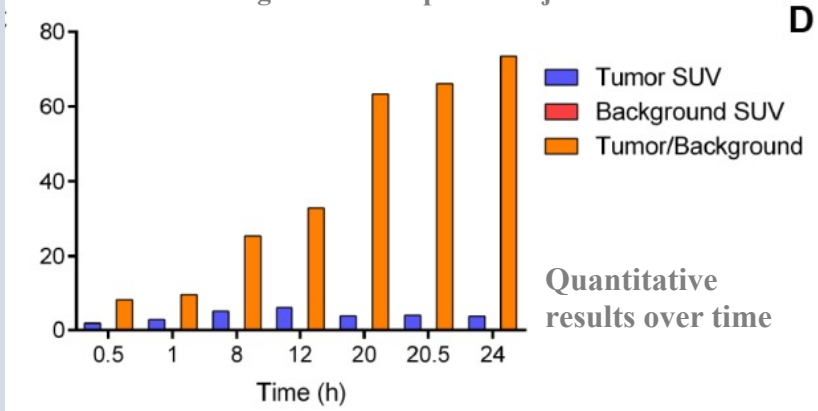
Representative coronal PET image of healthy human volunteer injected with ^{64}Cu-EB-RGD at 1, 8, and 24 h p.i.

Well Tolerated, no adverse events

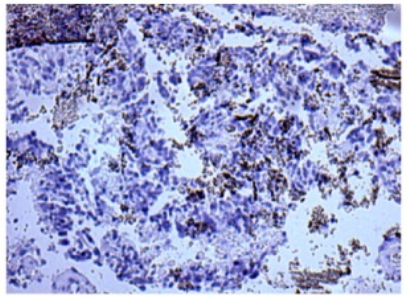
Glioblastoma Multiforme Patient



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



Quantitative results over time



Immunohistology of integrin $\alpha_v\beta_3$ levels in the tumor

Provided by Zhang J, et al, Peking Union Medical College Hospital (PUMCH)

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

EBRGD™ (^{177}Lu-DOTA-EB-RGD) Conclusions

- Conjugation of EB to DOTA-RGD resulted in a significant increase in tumor uptake and tumor retention as shown with ^{177}Lu/^{90}Y/^{64}Cu
- A single dose of ^{177}Lu-EB-RGD (18.5 MBq) completely eradicated the tumors in PDX$_{\alpha v\beta 3}$ NSCLC mouse model with no sign of tumor recurrence during the observation period
- ^{64}Cu-EB-RGD showed prolonged circulation half-life and enhanced tumor accumulation in GBM patient
- Concurrent blockade of PD-1/PD-L1 combined with ^{177}Lu-EB-RGD improves overall survival and long-term tumor control in a colorectal cancer model

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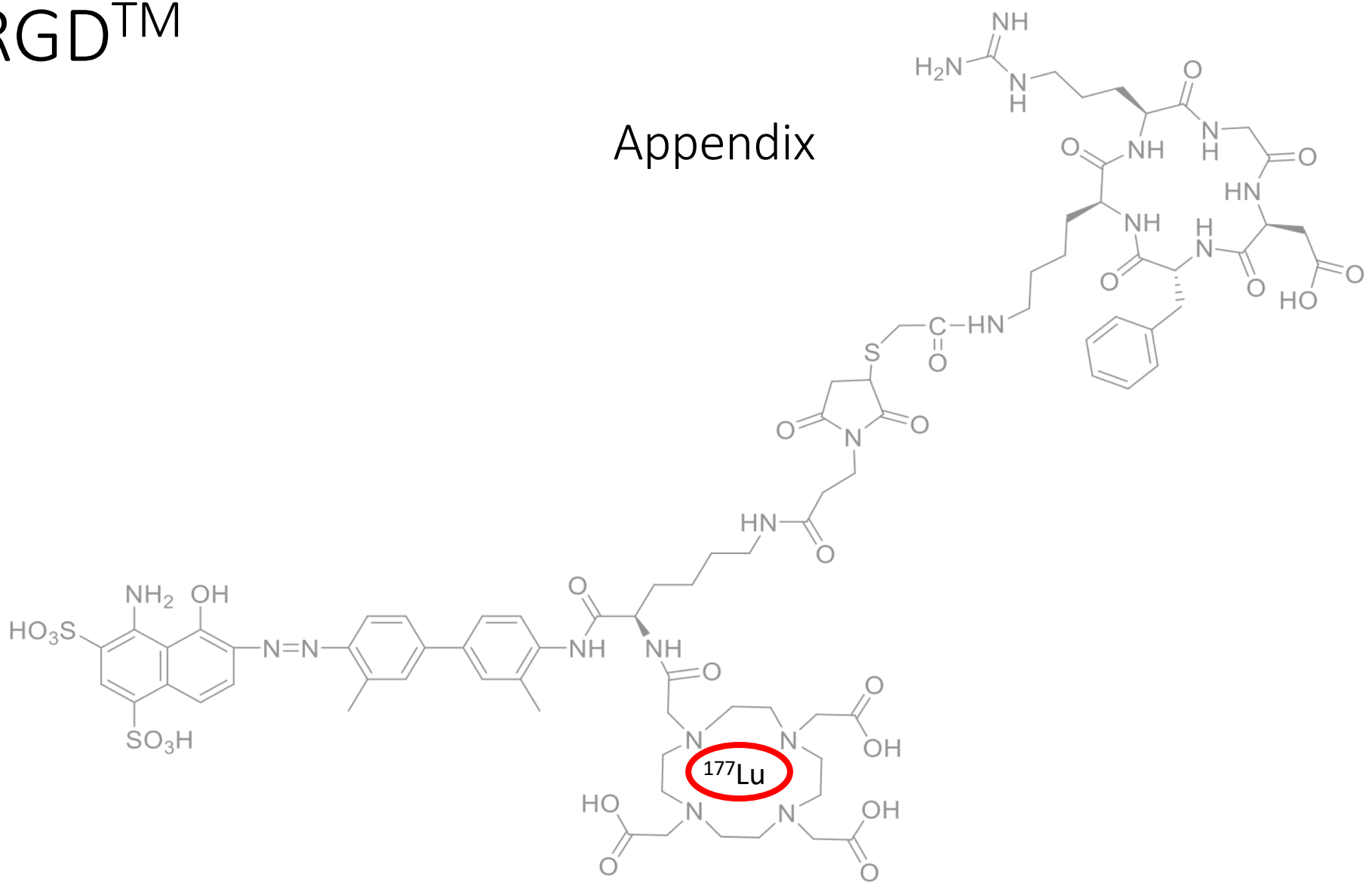
EBRGD™

Appendix



= ^{177}Lu, ^{90}Y, ^{67}Cu/^{64}Cu (NOTA chelator), & other possible radioisotopes

EBRGD^{TM}

Appendix

- Potency of radiolabeled EBRGD IC_{50}~10^{-7}M (74.1 nM [NOTA-EB-RGD) & 76.6 nM [DOTA-EB-RGD] see ***Chen et al, 2017; Chen et al, 2017 Supplement Fig 2***

- Specificity of EBRGD is based on the cyclic pentapeptide, c(RGDfK):

IC50	Integrin
2.25 nM	αvβ3
55 nM	αvβ6
141 nM	α5β1
340 nM	αvβ5
5,200 nM	αvβ8
>10,000 nM	αIIbβ3

see ***Kapp et al. A comprehensive evaluation of…ligands for RGD-binding integrins. Sci Rep 2017; 7: 39805***