



Molecular Targeting Technologies, Inc.

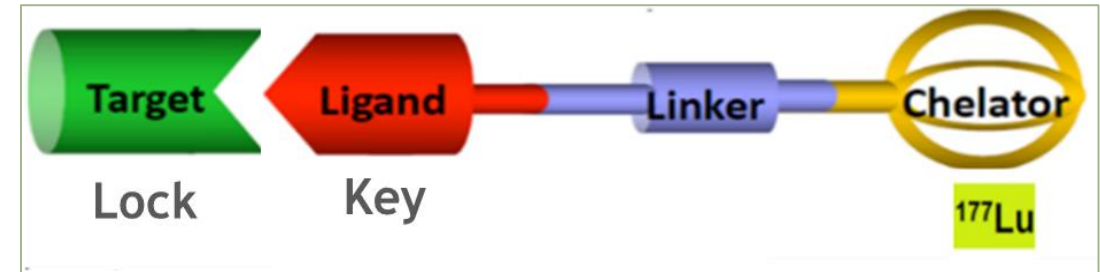
www.mtarget.com

EvaThera Theranostics

A novel targeted peptide radiotherapeutic platform for SSTR2 and $\alpha_v\beta_3$ integrin expressing tumors

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EvaThera Platform

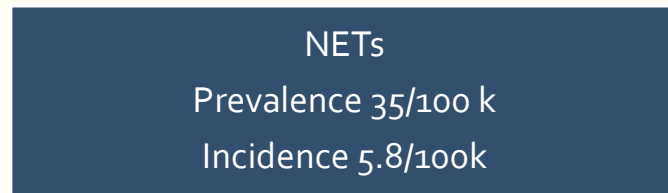


PLATFORM DRUG	PROBABLE INDICATIONS	TARGET RECEPTOR (high tumor density vs. normal organ expression)	LIGAND (agonist/antagonist/inhibitor, affinity/specificity, metabolic stability)	RADIONUCLIDES (emission)
EBTATE	NET, Hurthle cell thyroid, nasopharyngeal, pancreatic, renal and others	Somatostatin receptor type 2 (SSTR-2)	TATE - agonist, high affinity, high specificity, stable	¹⁷⁷ Lu [low energy, short range (2.2mm) gamma particle] ²²⁵ Ac [very high energy, very short range (40-100μm), alpha particle]
EBRGD	Upregulates PD-L1 expression, enhances immunotherapy efficacy. Targets glioblastoma multiforme, non-small cell lung, ovarian, breast, bone, prostate & others.	$\alpha_v\beta_3$ integrin	RGD - inhibitor, high affinity, high specificity, stable	¹⁷⁷ Lu [low energy, short range (2.2mm) gamma particle] ²²⁵ Ac [very high energy, very short range (40-100μm), alpha particle]

EBTATE for Neuroendocrine Tumors

What are NETs?

- Heterogeneous group of tumors originating from the cells of endocrine and nervous system.
- **~80% of NETs overexpress somatostatin receptors (particularly SSTR2).**



Foregut

Lung, Thymus, Esophagus, Stomach, Duodenum, Pancreas

Midgut

Small bowel, appendix, Ileum, cecum, proximal colon

Hindgut

Distal colon and rectum

Treatment options

- Surgery (curative vs debulking)
- Radiofrequency ablation
- Chemo-embolization
- **Somatostatin analogue (hormonal treatment)**
- Chemotherapy or other medical therapy (targeted kinase inhibitors)
- **Radionuclide therapy**

Opportunities for SSAs

- Diagnosis/staging through radiolabeled somatostatin analogs (SSA)
- Treatment of p-NETs with SSA like Sandostatin LAR (Novartis, market leader with US\$1.7bn sales in 2014) or Somatuline (Ipsen)
- **2019 Lutathera® approval (Novartis acquired AAA for \$3.9 Bn) marrying both SSA and radionuclide therapy**

^{177}Lu -dotatate (Lutathera[®])

- Lutathera[®] (^{177}Lu -dotatate) received regulatory approval in the European Union (September 2017) and in the US (January 2018) against rare gastroenteropancreatic neuroendocrine tumors (NET)
- Sales of Lutathera[®] hit \$441 million in 2019 with a 31% jump in Q4 alone, indicating a strong growth trajectory for the radiotherapy. Analysts predict peak sales between \$1 billion and \$2 billion.
- Global NET market is projected at \$5.3 B by 2028 (Data Bridge)

Improving upon ^{177}Lu -dotatate

Rapid clearance

^{177}Lu -dotatate clears rapidly through the kidneys with a blood **half-life of a few hours**

Low response rate

19% GEP-NET patients show complete or partial response to ^{177}Lu -dotatate. Low complete remission rate (~1%)

Admin burden

Higher activity and multiple injections are needed for optimal therapeutic effect.

Safety

Multiple injections can cause high kidney toxicity and partial/high bone marrow toxicity. Amino acid infusion is needed to reduce toxicity causes nausea and vomiting

EvaThera Platform

Theranostics 2018, Vol. 8, Issue 3

735



Theranostics

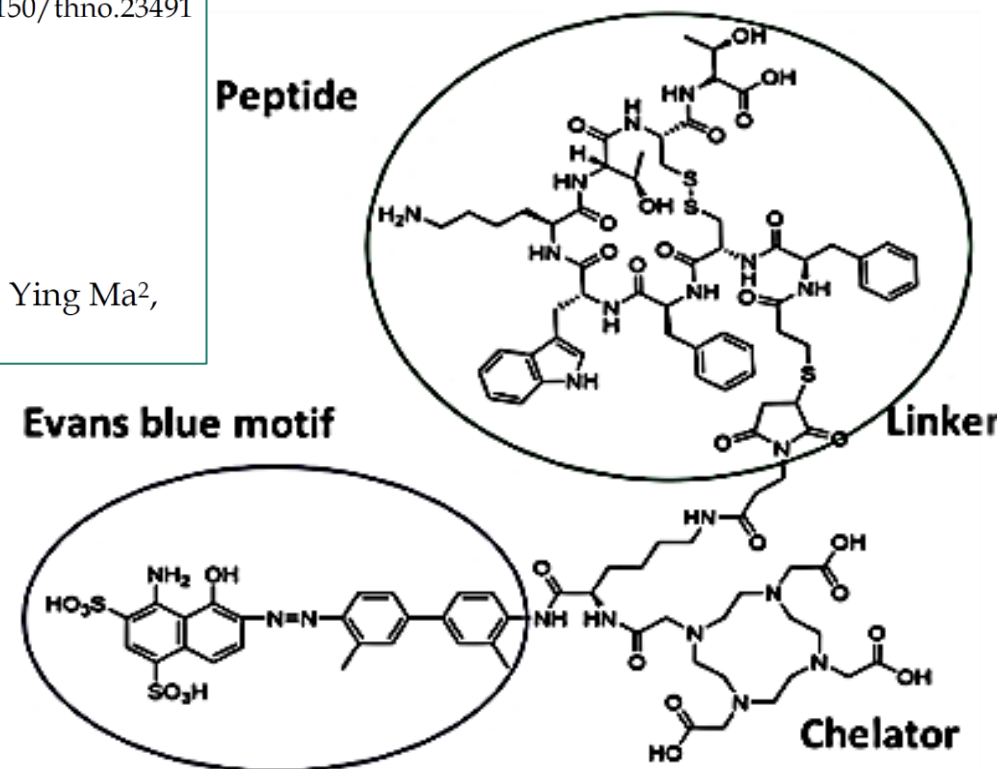
2018; 8(3): 735-745. doi: 10.7150/thno.23491

Research Paper

Evans Blue Attachment Enhances Somatostatin Receptor Subtype-2 Imaging and Radiotherapy

Rui Tian^{1,2}, Orit Jacobson²✉, Gang Niu², Dale O. Kiesewetter², Zhantong Wang², Guizhi Zhu², Ying Ma², Gang Liu¹ and Xiaoyuan Chen²✉

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March 2021 news on EBTATE clinical studies

Peptide Receptor Radionuclide Therapy of Late-Stage Neuroendocrine Tumor Patients with Multiple Cycles of ^{177}Lu -DOTA-EB-TATE

Qingxing Liu^{1,2*}, Jie Zang^{1,2*}, Huimin Sui^{1,2}, Jiakun Ren^{1,2}, Hua Guo^{1,2}, Hao Wang^{1,2}, Rongxi Wang^{1,2}, Orit Jacobson³, Jingjing Zhang⁴, Yuejuan Cheng^{†5}, Zhaohui Zhu^{†1,2}, and Xiaoyuan Chen^{†3}



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New Treatment Proves More Effective and Less Toxic for Neuroendocrine Tumor Patients

March 19, 2021

Reston, VA—A new treatment for late-stage neuroendocrine tumors (NETs) has been found to be more effective and have fewer side effects than the current standard of care, according to research published in the March issue of *The Journal of Nuclear Medicine*. The novel peptide receptor radionuclide therapy holds promise to reduce mortality among NET patients and decrease the financial burden of their continual treatment.

NETs are a diverse group of tumors that originate from the neuroendocrine system, which is responsible for regulating hormones throughout the body. The number of people who are diagnosed with NETs is growing; the incidence of NETs increased 6.4-fold from 1973 to 2012. However, because they are rare, varied, and slow growing, the diagnosis of a NET can be delayed up to seven years. As a result, more than 50 percent of NET cases are at an advanced stage at the time of diagnosis.

The current standard of care for late-stage NET patients is peptide receptor radionuclide therapy with ^{177}Lu -DOTATATE, which is flushed from a patient's system rapidly after administration. Preclinical studies found that if a special dye (Evans blue) is added to the ^{177}Lu -DOTATATE, the treatment can last longer in the body and be more effective. In this study, researchers sought to determine what dose of the modified therapy, known as ^{177}Lu -DOTA-EB-TATE, is safest and produces the best tumor response.

RELATED CONTENT

- With Advent of New Treatments, PET Imaging Adds Valuable Information to Brain Metastasis Monitoring
- A Partial Win: Humana Reverses PET/CT Non-Coverage Policy
- SNMMI & Partners Urge Congress to Expand MPFS Relief into 2022
- New Radiotracer Safe and Effective for Imaging Early Rheumatoid Arthritis
- Grants, Awards, and Scholarships

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A great March at #MTTI! We obtained FDA approval for our IND application enabling a Phase I clinical study of the safety and dosimetry of our lead product, #EBTATE (^{177}Lu -DOTA-EB-TATE) in patients with #neuroendocrinetumors (NET).

<https://lnkd.in/e67DJdc>



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NEWS RELEASE 22-MAR-2021

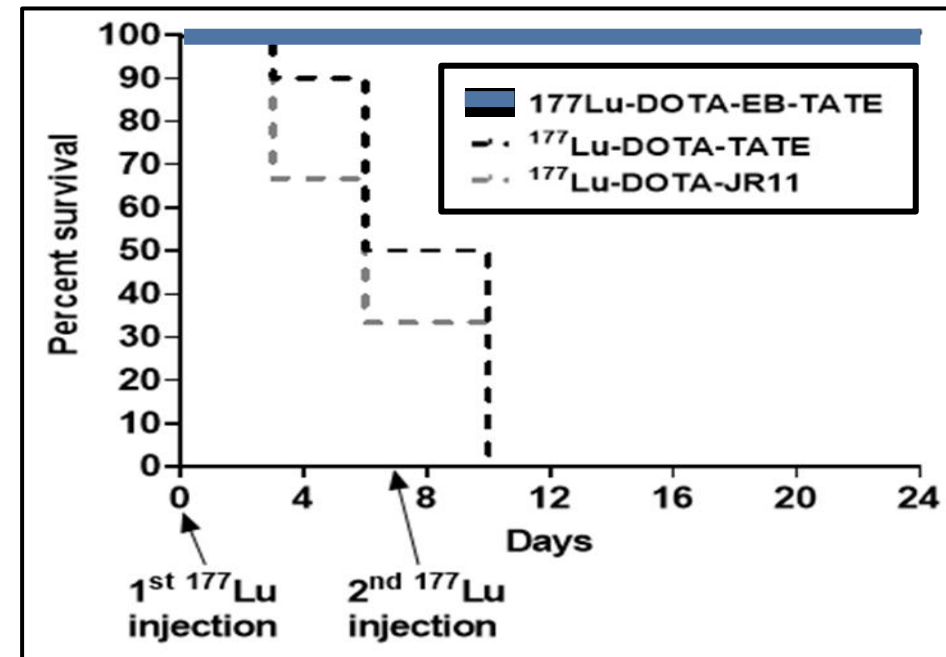
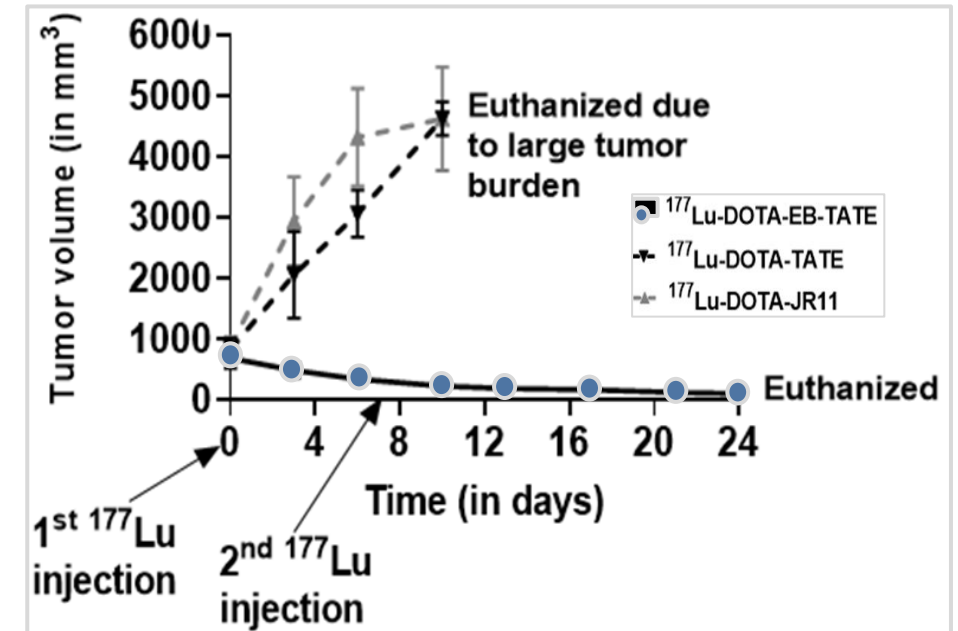
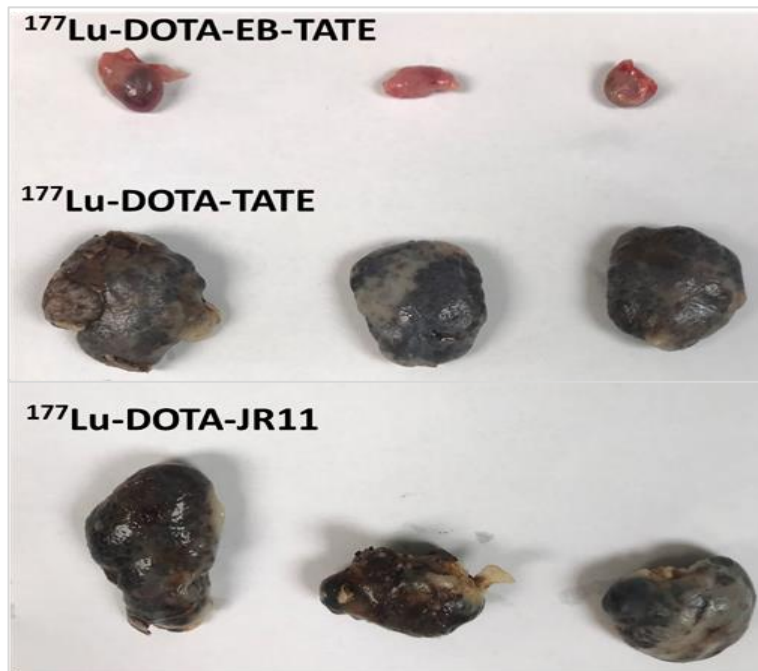
New treatment proves more effective and less toxic for neuroendocrine tumor patients

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PRECLINICAL EFFICACY OF EBTATE VS. ^{177}Lu -DOTATATE in PANCREATIC CANCER

EBTATE treated AR42J mice responded to treatment after 2 wk post-therapy. Tumors of mice treated with ^{177}Lu -dotatate continued to progress and the mice had to be euthanized within 10 days.

Provided by Joanna Klubo-Gwiezdzinska, MD of NIDDK of NIH



EBTATE for Hürthle cell thyroid carcinoma (HTC)

- 3-5% of thyroid malignancies, ~1,600 in the US per annum.
- Poor, long-lasting remission and/or survival from conventional radioactive iodine (^{131}I) treatment, unlike non-HTC thyroid cancer.
- HTC patients have high SSTR2 expression and high uptake of ^{68}Ga -DOTA-TATE (SSTR2 Marker).
- *In vivo* mouse studies with EBTATE extended survival and reduced tumor size in animal models with high SSTR2 tumor expression (AR42J) but not with low SSTR2 (FTC133) expression. Confirmed significantly greater diagnostic and therapeutic efficacy vs. Lutathera or DOTA-JR11.
- NIH funded Phase II trial proposed mid-2022.

EBTATE Advantages

- In a head-to-head *in vivo* comparison, EBTATE showed improved anti-tumor efficacy versus ^{177}Lu -dotatate
- Early clinical data showed that EBTATE is safe and achieved objective responses after a single injection
- Multiple cycles of escalating doses of EBTATE seem to be well tolerated and were effective in tumor control.
- EBTATE should also target Hürthle cell thyroid cancer (an unmet medical need) and nasopharyngeal cancer (significant in SE Asia)
- EBTATE may not need pre-PRRT amino acid treatment.

EBRGD enhances immunotherapy efficacy

Premise

- Current checkpoint inhibitor immunotherapies have low response rates.
- Multiple studies on radiation, external beam therapy, chemotherapies, vaccines...show PD-L1 upregulation enhances immunotherapeutic response.

Hypothesis/Study

- ^{177}Lu -EBRGD targets and kills tumors
- Radiation upregulates PD-L1
- Mice with colorectal cancer xenografts were treated with ^{177}Lu -EBRGD and anti-mouse PD-L1 mAb.

Results

- ...EBRGD targeted radionuclide therapy in combination with an anti PD-L1 mAb...
- led to an acute increase in PD-L1 expression on T cells, and
 - EBRGD in combination with $\alpha\text{PD-L1}$ mAb stimulated the infiltration of CD8+ T cells,
 - **which improved local tumor control, overall survival and protection against tumor rechallenge.**

EBRGD enhances immunotherapy efficacy

Theranostics 2019, Vol. 9, Issue 25

7948



Theranostics

2019; 9(25): 7948-7960. doi: 10.7150/thno.39203

Research Paper

Integrin $\alpha_v\beta_3$ -targeted radionuclide therapy combined with immune checkpoint blockade immunotherapy synergistically enhances anti-tumor efficacy

Haojun Chen^{1*}, Liang Zhao^{2*}, Kaili Fu², Qiuming Lin², Xuejun Wen³, Orit Jacobson⁴, Long Sun¹, Hua Wu¹, Xianzhong Zhang³✉, Zhide Guo³✉, Qin Lin²✉, Xiaoyuan Chen⁴✉

...TRT [EBRGD targeted radionuclide therapy] led to an acute increase in PD-L1 expression on T cells, and TRT in combination with α PD-L1 mAb stimulated the infiltration of CD8+ T cells, which improved local tumor control, overall survival and protection against tumor rechallenge.

EBRGD enhances immunotherapy efficacy

Group A: Control

Saline (D 0)



Group B: ^{177}Lu -TRT

^{177}Lu -TRT (D 0)



D0



Group C: Immunotherapy

α PD-L1 mAb (D 0, 3, 6)



D0

D3

D6



Group D: Concurrent therapy

^{177}Lu -TRT (D 0)



D0

D1

D4

D7



D11

D14

D17



Group E: Sequential therapy

^{177}Lu -TRT (D 0)



D0

D11

D14

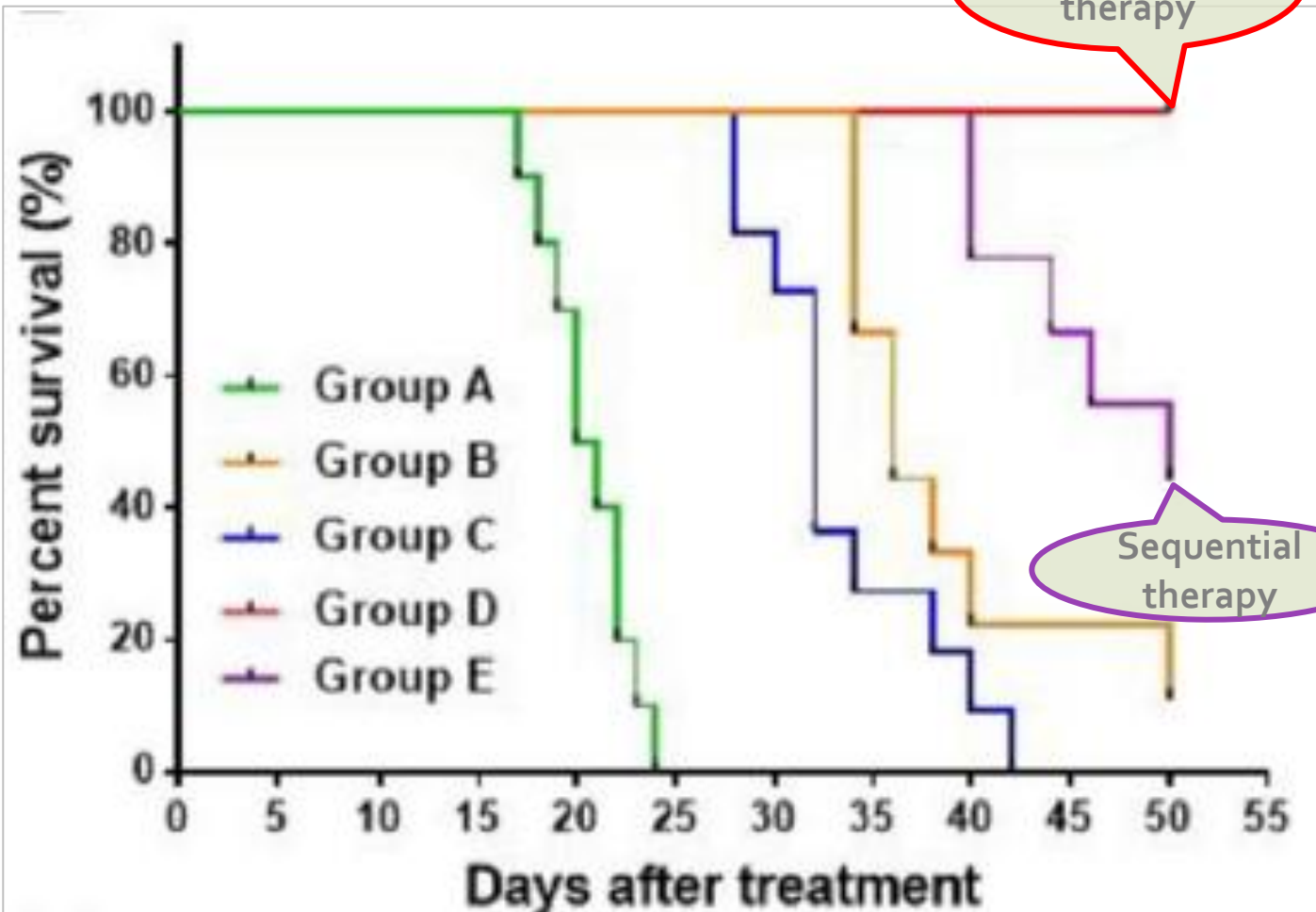
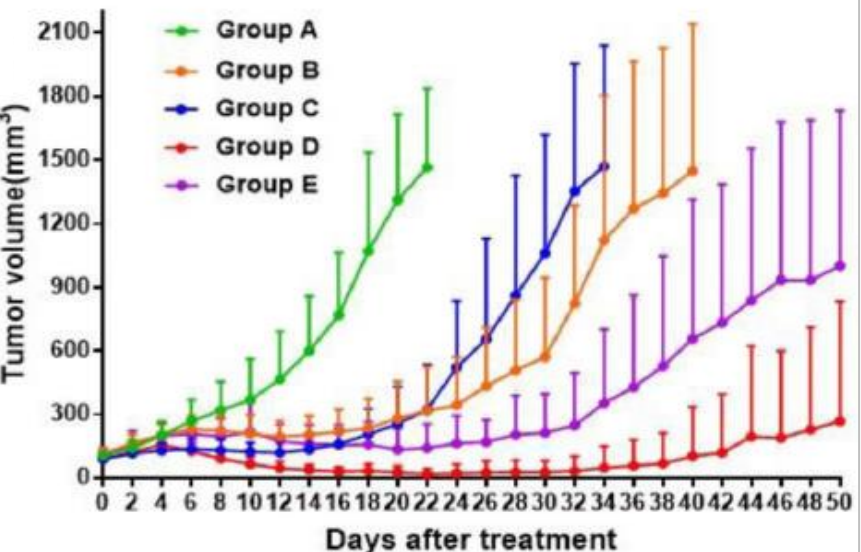
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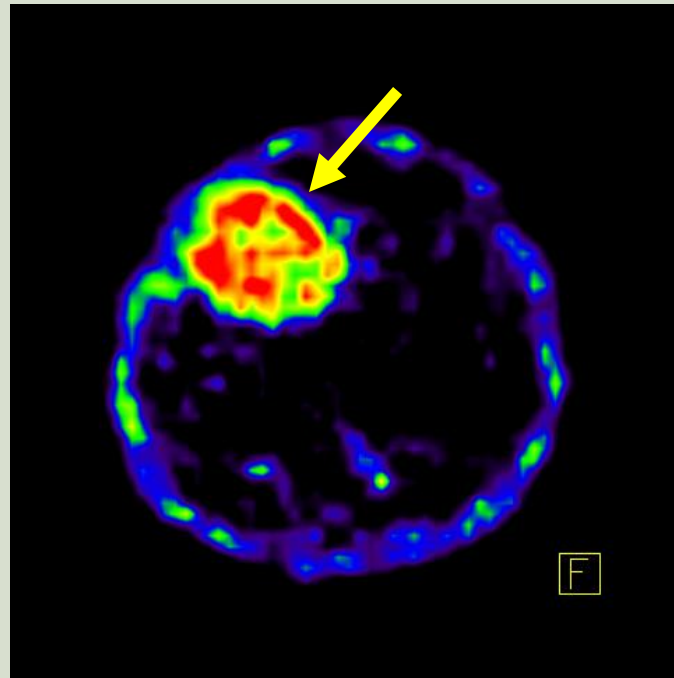
Concurrent therapy

Sequential therapy

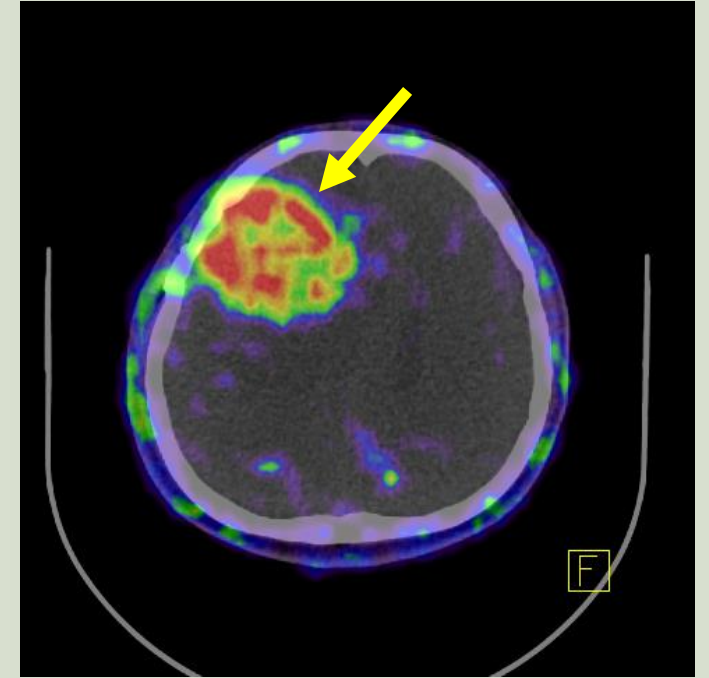
^{64}Cu -EBRGD diagnostic targets integrin $\alpha\nu\beta_3$ in GBM (Clinical summary)

Axial PET and PET/CT slices of glioblastoma multiforme (GBM) patient injected with ^{64}Cu -EBRGD at 24 h p.i.

Glioblastoma Patient



^{64}Cu -EBRGD
24h p.i.



^{64}Cu -EBRGD
24h p.i.

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

Summary

EvaThera platform

- broad application across targeting peptides, indications, radionuclides...
- safe & effective
- excellent IP protection

EBTATE

- demonstrated improvement over ^{177}Lu -dotatate
- significant market potential
- clinical trials are in progress

EBRGD

- enhances immunotherapy efficacy
- demonstrated GBM targeting

Contact

MTTI is seeking corporate partners to advance the EvaThera platform for two orphan drugs targeting Hürthle cell thyroid cancer and glioblastoma multiforme indications

Business development contact for **EvaThera**

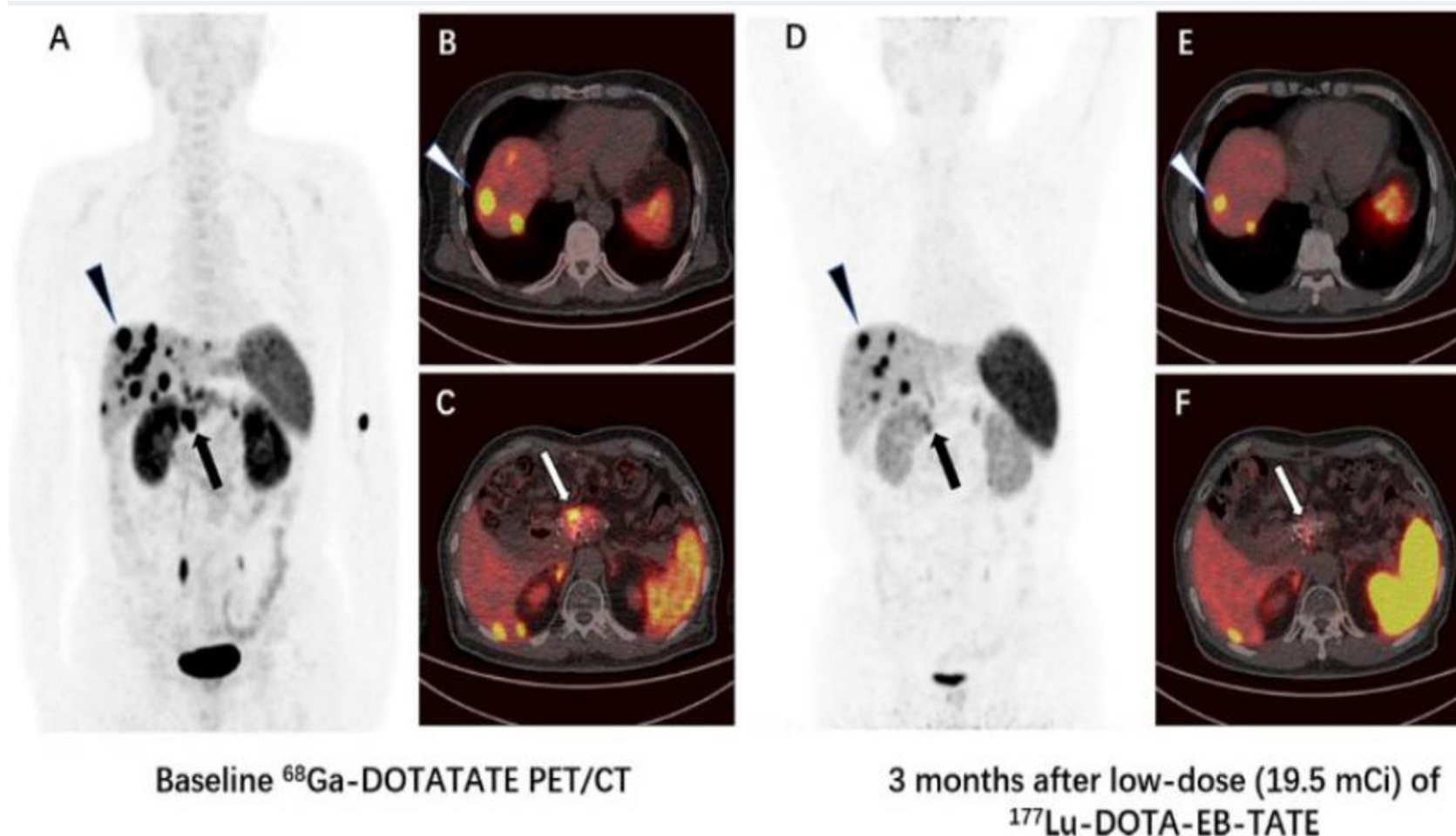
Chris Pak
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Ji Li, Ph.D.
COO/CFO
jli@mtarget.com

Tel: 610-738-7938

Tumor size reduction observed in patients after a single injection of EBTATE (20 mCi) (One tenth dose of ^{177}Lu -dotatate of 200 mCi)



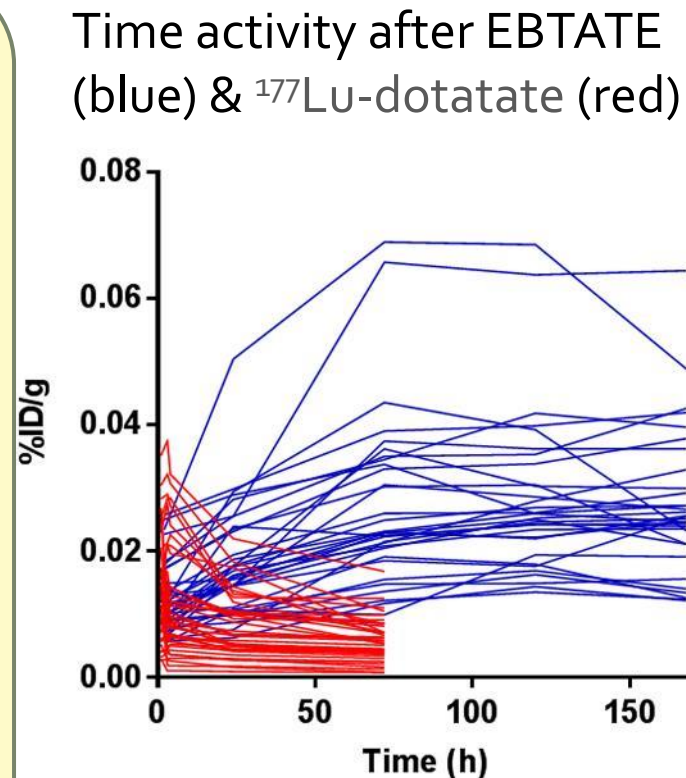
Comparison of ^{68}Ga -DOTA-TATE PET/CT images:

- immediately before (A-C)
- 3 months after (D-F)

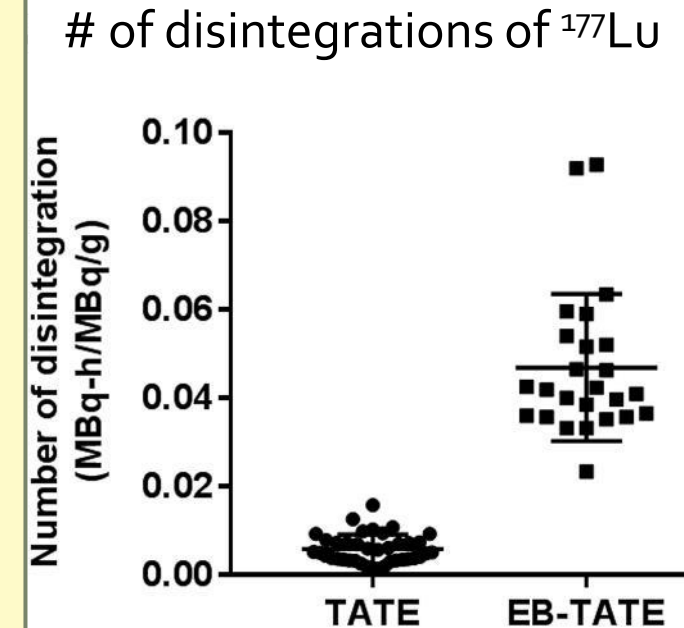
The SUV_{max} of the primary tumor in pancreas decreased from 26.7 to 13.0 (arrow), and the SUV_{max} of the highest-uptake liver metastasis decreased from 50.6 to 28.6 (triangle).

EBTATE (MTTI) demonstrated improved PK/PD vs. ^{177}Lu -dotatate

- EBTATE reached peak slower, and had a prolonged plateau compared to ^{177}Lu -dotatate



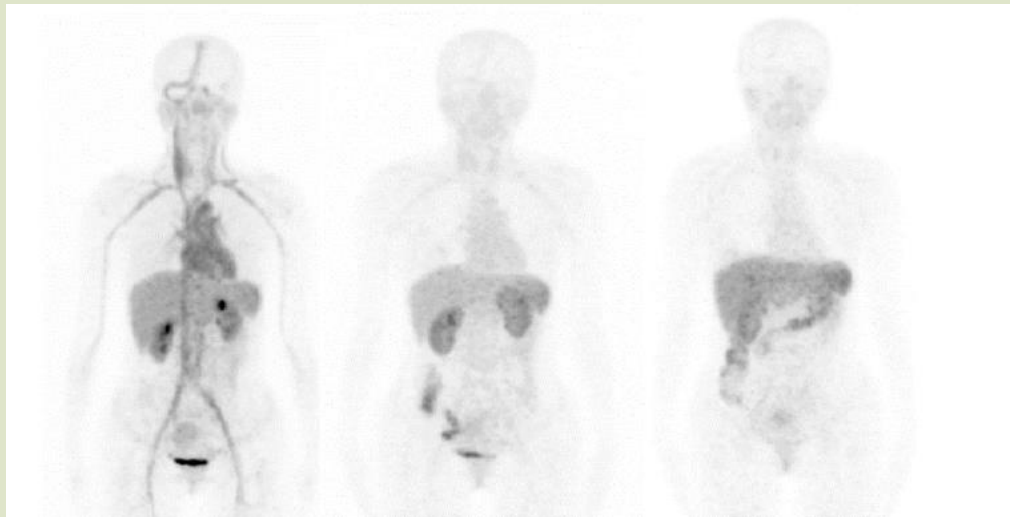
- EBTATE showed 800% increase of lesion radiation counts vs. Lutathera



^{64}Cu -EBRGD (Clinical summary)

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).



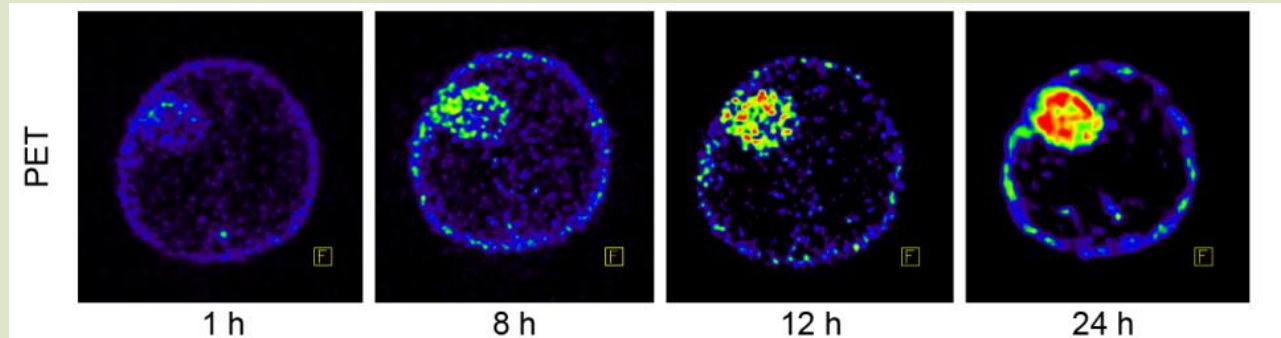
1h

8h

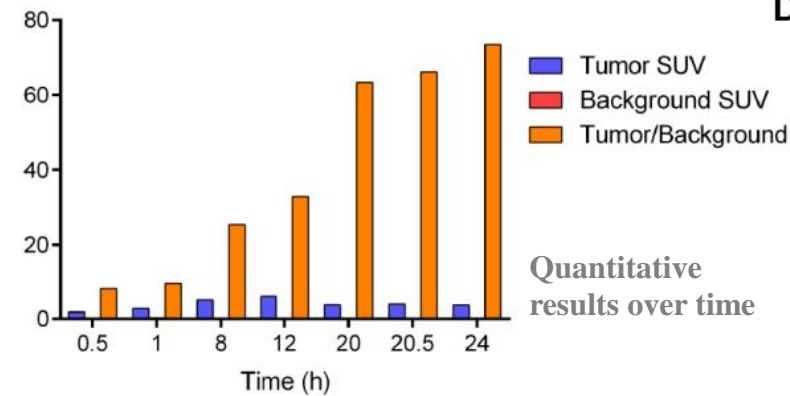
24h

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

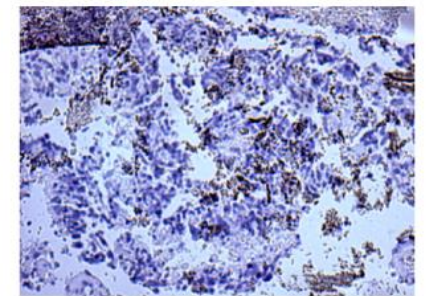
Glioblastoma Multiforme Patient



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



D



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

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