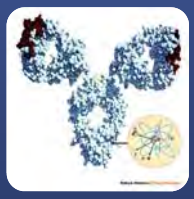
Targeted molecular radiotherapy

presented by Janina Baranowska-Kortylewicz, Ph.D.
Department of Radiation Oncology
J. Bruce Henriksen Cancer Research Laboratories
University of Nebraska Medical Center

What is molecular radiotherapy?

Therapeutic approach that uses radionuclides or radiolabeled drugs to kill cancer cells.

What is molecular radiotherapy?



Delivery of radioactivity to tumor takes advantage of some aspect of tumor physiology to provide targeted accretion of radioactivity in tumor cells or in their immediate vicinity.

MRT: Interdisciplinary approach

- Radiochemistry
- Nuclear medicine
- Radiation oncology
- Internal medicine
- Medical physics
- Radiation safety

Targets for MRT

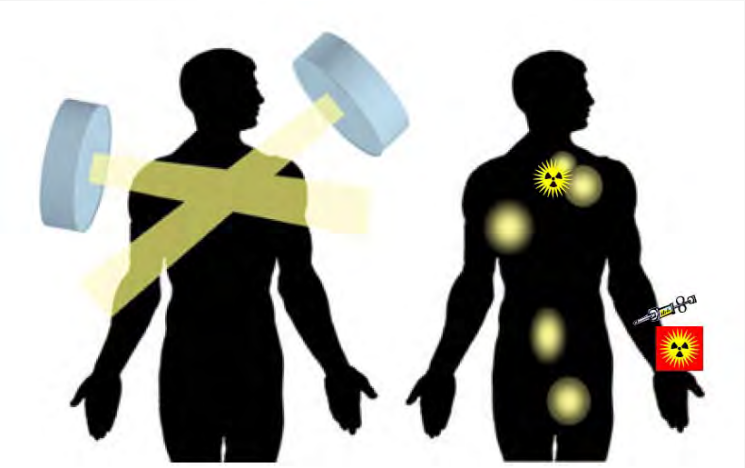
- tumor viability
- tumor proliferation
- cell membrane turnover
- antigen-antibody systems
- peptides and their receptors
- other ligands and their receptors

Radiation therapy and Targeted molecular radiotherapy:

…

complementary modalities

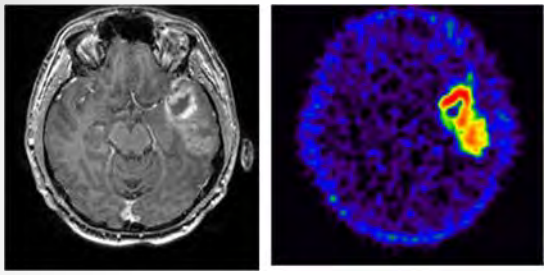
RT and targeted MRT



requires knowledge of tumor location

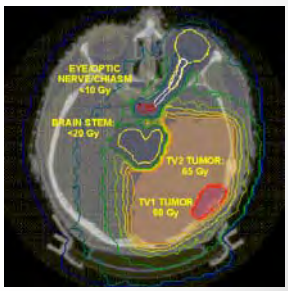
requires knowledge of tumor biology

Targeted molecular radiotherapy



http://www.cambridgecancercentre.org.uk/users/fia20; contributed by Dr. Franklin Aigbirhio.

Intensity modulated radiation therapy

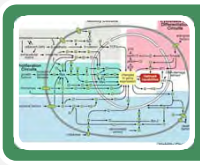


http://www.spectral.com/imrt.shtml

Targeted MRT

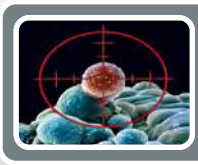
Heterogeneity of cancer genome

- targeting cancer subsets
- targeting cancer mutations



Epigenetics

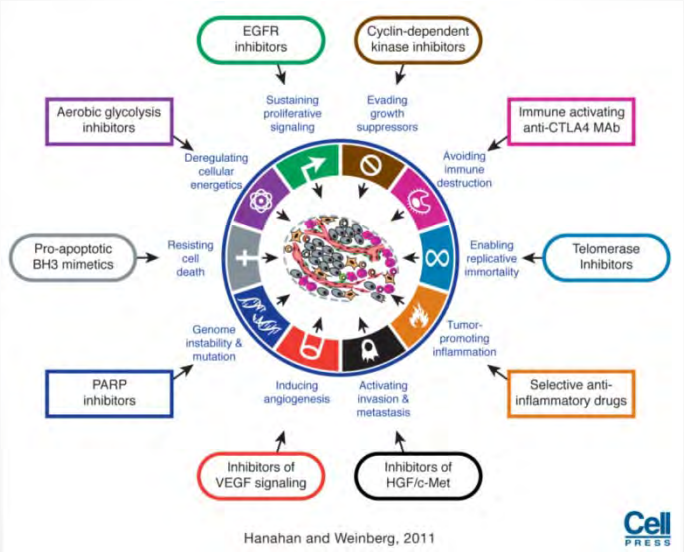
- targeting cancer subsets
- targeting cancer mutations



Cancer stem cells

Circulating metastasis-initiating cells

Therapeutic targeting of cancer



Merits of targeted MRT

Targeted Molecular Radiotherapy

Treatment can be individualized based on tumor molecular profile, confirmed by imaging, and complemented by genetic evaluation

tMRT

Molecular imaging identifies the most appropriate therapeutic targets

Theranostic approach guides the selection of radionuclides

Dosimetry determines the best radionuclide and targeting molecule for tumor eradication while sparing normal tissues

Merits of targeted MRT

tMRT

Customized radiotherapeutic cocktails are conceivable containing

- radionuclides emitting different radiation
- molecular carriers with diverse biological properties
- multiple tumor-associated molecular targets

Noninvasive monitoring of the distribution of the targeted radionuclide

Multiple treatments with non-immunogenic radiotherapeutics

Adaptive MRT

treat
- patient is initially treated with targeted MRT using a high-energy β-emitting radionuclide to reduce tumor volume

image
- molecular imaging with the same vector evaluates tumor responses and helps to adjust the next treatment to the altered molecular status of the tumor

decide
- if response to MRT changes molecular target population, alter the molecular vector or radionuclide, as needed

treat
- subsequent treatment for residual disease with an α-emitting radionuclide with a more focal irradiation

The U.S. FDA-approved radiotherapeutics

Agent	Trade name	Indications
sodium [^{131}I]iodide	HICON™	treatment of carcinoma of the thyroid
[^{153}Sm]samarium lexidronam	Quadramet®	relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan
[^{89}Sr]strontium chloride	Metastron™	relief of bone pain in patients with painful skeletal metastases that have been confirmed prior to therapy
[^{223}Ra]radium chloride)	Alpharadin®	treatment of CRCP patients whose cancer has spread to the bone
[^{32}P]chromic phosphate	Phosphocol ®	intraperitoneal or intracavitary for treatment of peritoneal or pleural effusions caused by metastatic disease

The U.S. FDA-approved radiotherapeutics

Agent	Trade name	Indications
[^{90}Y] yttrium ibritumomab tiuxetan	Zevalin®	●treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma ●treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy
[^{131}I]tositumomab	BEXXAR®	CD20 antigen-expressing relapsed or refractory, low grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with Rituximab-refractory non-Hodgkin's lymphoma
^{123}I-MIBG	Iobenguane®	primary or metastatic pheochromocytoma or neuroblastoma

When MRT is applicable?

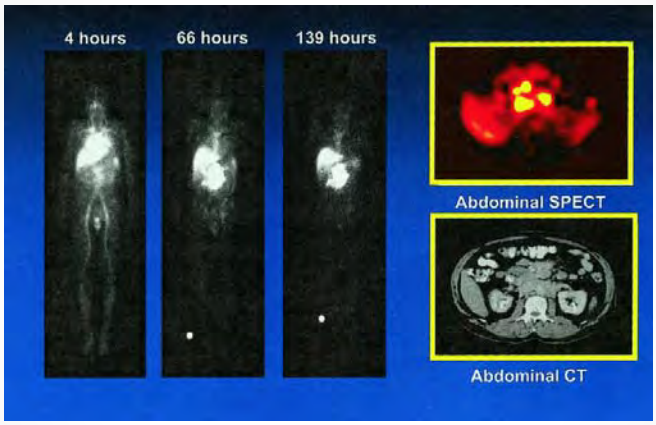
1. **Metastatic disease**
2. **Minimum residual disease**
3. **Microscopic disease**

1. Metastatic disease ✓
2. Minimum residual disease
3. Microscopic disease

Metastatic disease

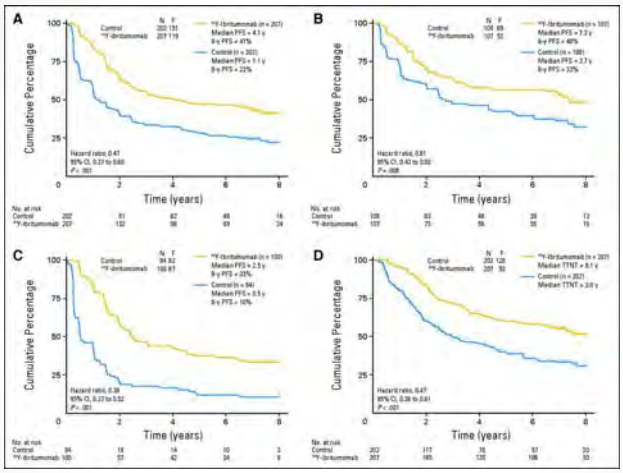
skeletal metastases

Zevalin



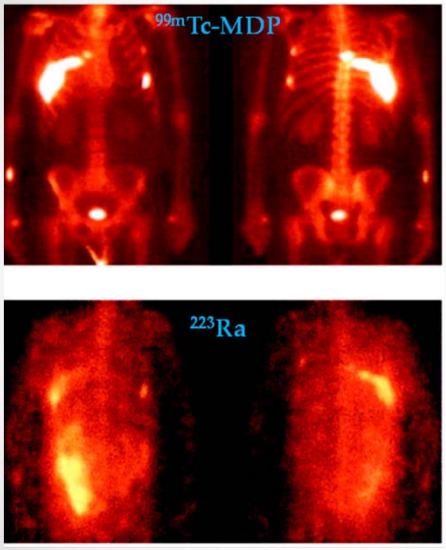
Radiation dosimetry results for zevalin radioimmunotherapy of rituximab-refractory non-hodgkin lymphoma. **Cancer.** Volume 94, Issue S4, pages 1349-1357, 12 FEB 2002 DOI: 10.1002/cncr.10305. http://onlinelibrary.wiley.com/doi/10.1002/cncr.10305/full#fig1

Zevalin: progression free survival



Morschhauser F et al. 90Yttrium-Ibritumomab Tiuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma: Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent TrialJCO 2013;31:1977-1983

JOURNAL OF CLINICAL ONCOLOGY ASCO

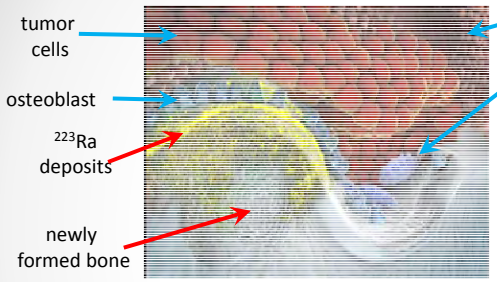


$^{223}RaCl_2$ Alpharadin α-emitter

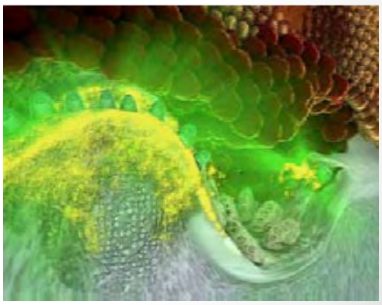
- bone seeking radiopharmaceutical
- first ever FDA-approved α-emitter
- fast track designation by the FDA August 23, 2011
- ^{223}Ra accumulates preferentially in osteoblastic metastases

Nilsson S et al. Clin Cancer Res 2005;11:4451-4459

Alpharadin



Alpharadin targets new bone in metastases...



...and irradiates adjacent tumor cells

$^{223}RdCl_2$

Discovered by Maria Skłodowska-Curie and her husband Pierre on December 21 in 1898.

Alpharadin approved 114 years later.

Used in cancer treatment in France since the 1900s, in Canada in the 1920s and 1930s

In USA, Howard Atwood Kelly, one of four founding physicians of Johns Hopkins Hospital, pioneered radium in cancer treatment in 1904

Kelly founded the privately owned Kelly Clinic in Baltimore, once the leading center for radiotherapy

Howard Kelly establishes gynecologic brachytherapy in the United States.
Aronowitz JN, Robison, RF. Brachytherapy. 2010; 9: 178–184. PMID 20022564.

Alpharadin

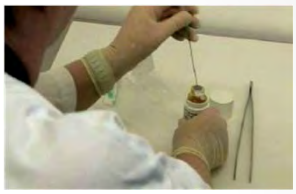
Benefits beyond palliation

- Increases overall survival >40% (p=0.017)
- Enhanced quality of life
- Side effect profile similar to placebo
- Effective pain control
- Targets osteoblastic/sclerotic phenotype lesions induced by bisphosphonate therapy
- Provides new option for Taxotere failures
- Provides new option for Taxotere ineligible patients
- Easy to use
- Effective in patients without other treatment options
- Keeps other therapeutic options open

Alpharadin is easy to use

Simple radiopharmacy

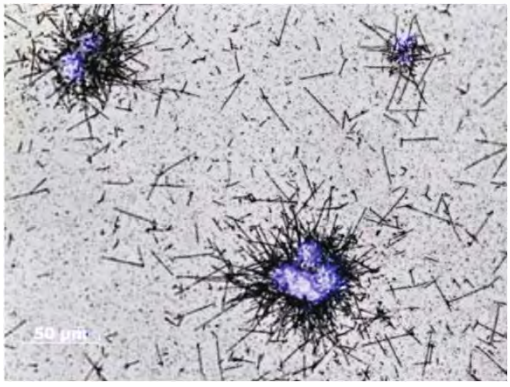
- easy logistics
- ready to use –no complex handling
- α particles stopped by syringe or vial wall
- administered dose is very low
- dose rates are very low



Simple Administration

- outpatient procedure
- IV injection –no time-consuming infusion
- no imaging or complex pre-medications
- no limits on interactions with others

^{227}Th-herceptin

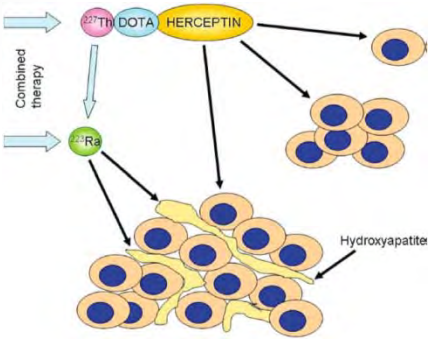


Microautoradiograph of individual α tracks from ^{227}Th-Herceptin bound to BT-474 microcolonies.

Cells were incubated with 10 kBq/ml ^{227}Th-Herceptin for 4 h.

Targeted High-LET Therapy of Bone Metastases. Ø.S. Bruland, D. Jostein, D.R. Olsen, R.H. Larsen
http://www.bruland.info/PDF/2008/Chapter_10.pdf

Dual targeted α therapy



- ^{227}Th-Herceptin targets and penetrates into clusters of tumor cells.
- As ^{227}Th decays, ^{223}Ra diffuses and rapidly targets hydroxyapatite in the sclerotic parts of the macroscopic skeletal metastasis

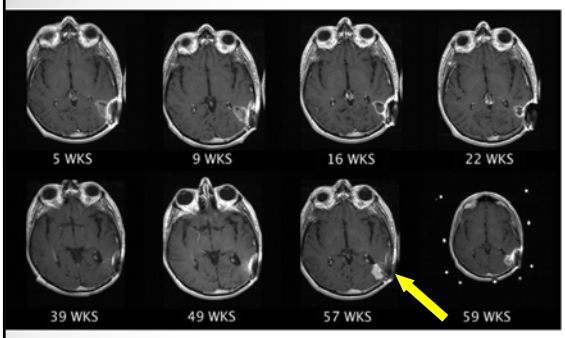
Targeted High-LET Therapy of Bone Metastases. Ø.S. Bruland, D. Jostein, D.R. Olsen, R.H. Larsen
http://www.bruland.info/PDF/2008/Chapter_10.pdf

1. Metastatic disease
2. Minimum residual disease ✓
3. Microscopic disease

Minimum residual disease

after surgical debulking

^{211}At-anti-tenascin



^{211}At-ch81C6

glioblastoma after surgical resection

Focal nodular enhancement 57 weeks after ^{211}At-ch81C6 therapy confirmed as recurrent anaplastic oligodendroglioma.

Zalutsky *et al.* Clinical experience with alpha-particle emitting 211At: treatment of recurrent brain tumor patients with 211At-labeled chimeric antitenascin monoclonal antibody 81C6. J Nucl Med. 2008; 49:30-8. PMID: 18077533.

1. Metastatic disease
2. Minimum residual disease
3. Microscopic disease ✓

Microscopic disease

biomarkers indicate progressing disease in the absence of the macroscopic evidence

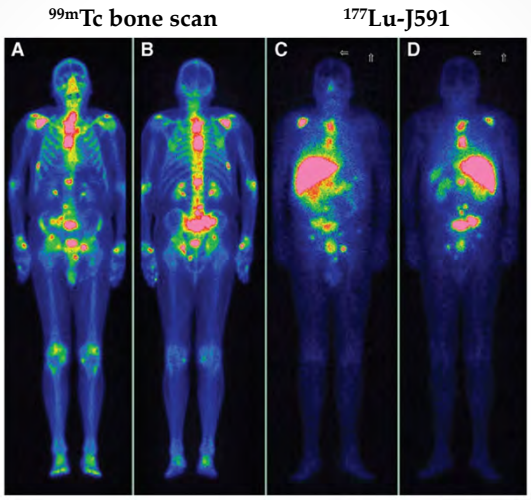
Microscopic disease

micrometastases

neoplasms that spread as microscopically thin sheets on compartmental surfaces

- ovarian carcinoma
- neoplastic meningitis

^{177}Lu-J591 anti-PSMA

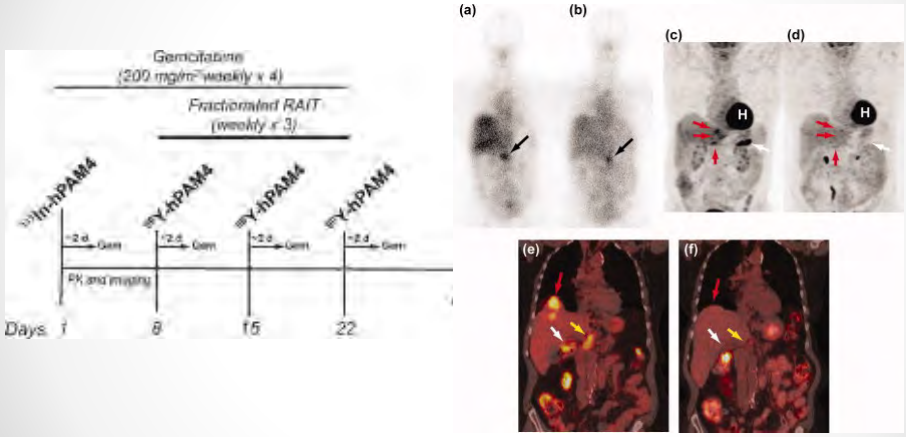


7 days after ^{177}Lu-J591 administration

Tagawa S T et al. Clin Cancer Res 2013;19:5182-5191

Clinical Cancer Research

Fractionated radioimmunotherapy with 90Y-clivatuzumab tetraxetan and low-dose gemcitabine is active in advanced pancreatic cancer



Cancer
Volume 118, Issue 22, pages 5497-5506, 8 MAY 2012 DOI: 10.1002/cncr.27592
http://onlinelibrary.wiley.com/doi/10.1002/cncr.27592/full#fig2

UNMC studies: androgen receptor-targeted MRT

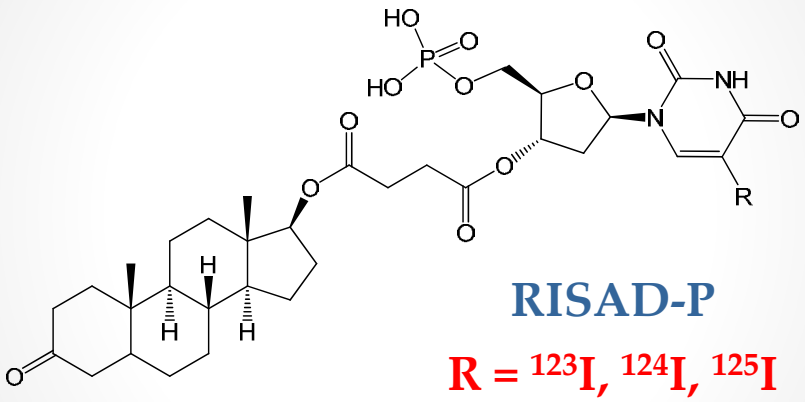
RISAD-P

Key points

Prostate cancer, after primary treatment, is largely driven by androgens and AR.

AR signaling remains the dominant growth pathway in prostate cancers that progress in the setting of low serum androgens.

AR-targeted MRT

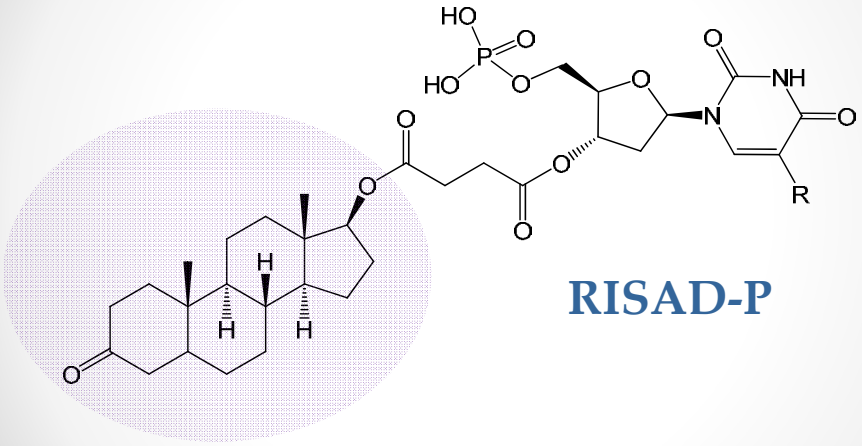


RISAD-P

R = ^{123}I, ^{124}I, ^{125}I

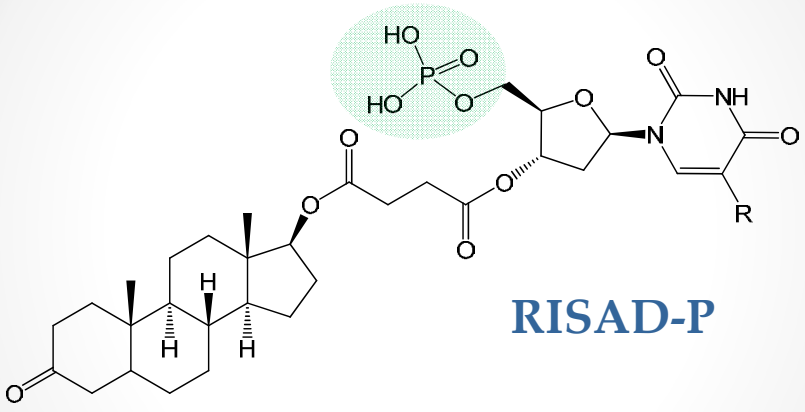
5-**R**adio**I**odo-3′-*O*-(17β-**S**uccinyl-5*α*-**A**ndrostan-3-one)-2′-**D**eoxyuridin-5′-yl mono**P**hosphate

AR binding



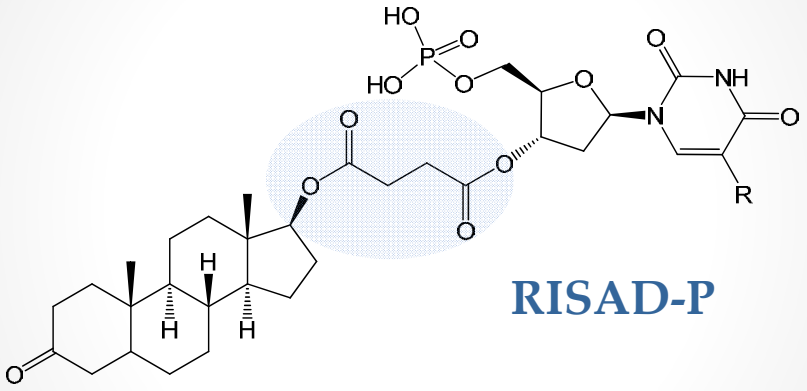
RISAD-P

Lock-in mechanism



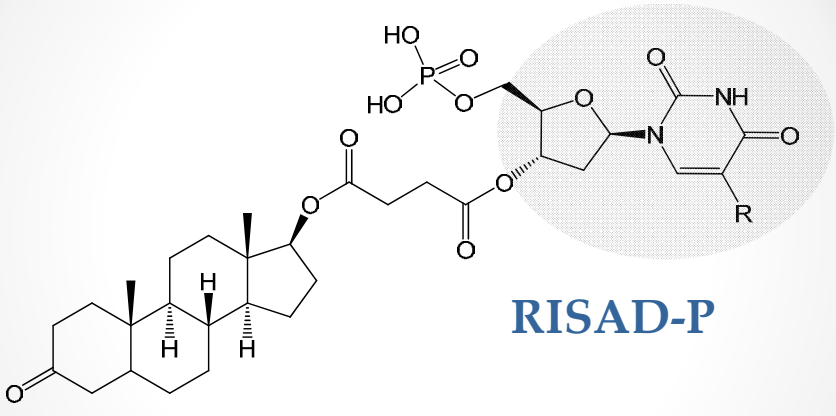
RISAD-P

Biodegradable linker



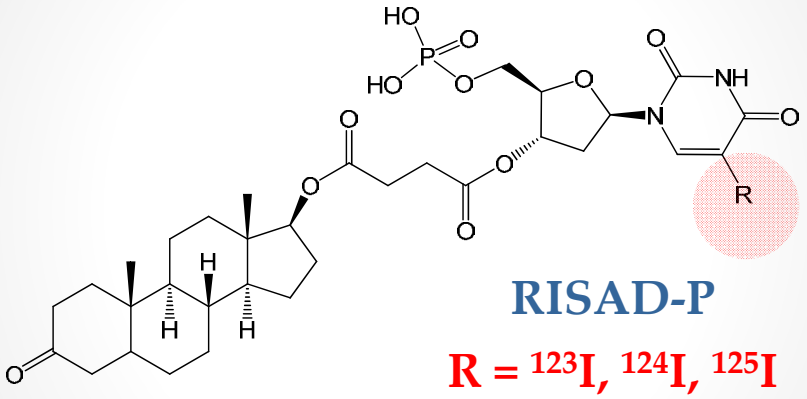
RISAD-P

DNA co-targeting



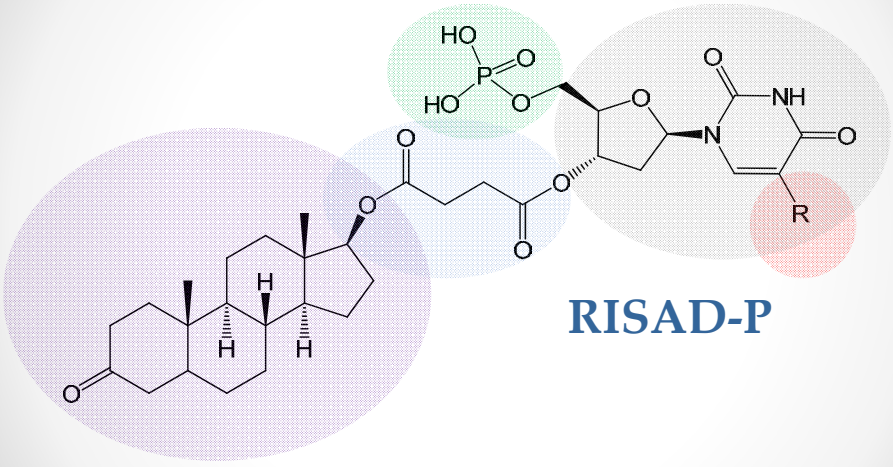
RISAD-P

Theranostic approach



RISAD-P

R = ^{123}I, ^{124}I, ^{125}I

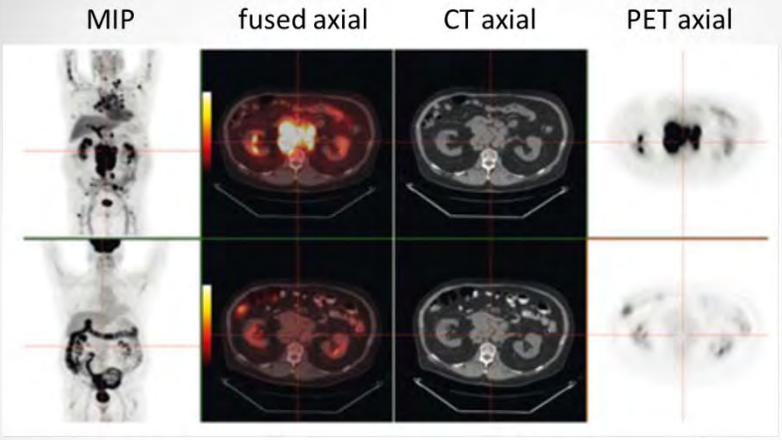


RISAD-P

Why AR targeted drug?

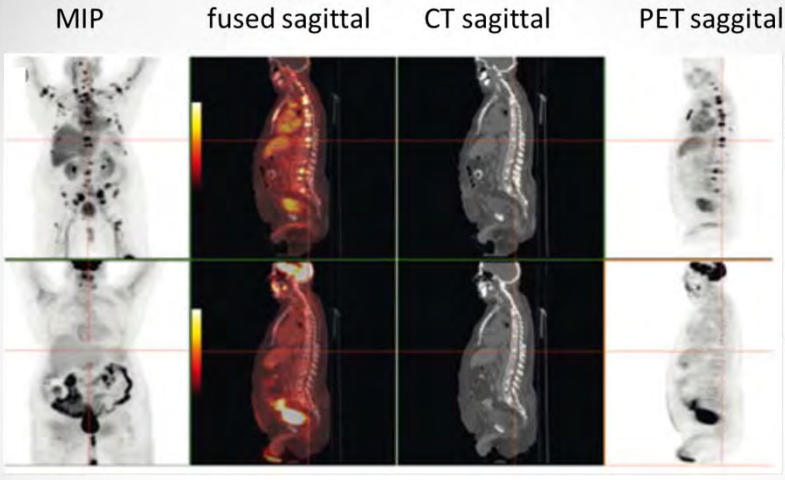
"...AR - targeted therapies will remain a central part of the treatment of advanced stage prostate cancer..."

Saylor PJ. Prostate cancer: The androgen receptor remains front and centre. Nat Rev Clin Oncol. 2013; 10:126-8. PMID: 23381000



16β-[^{18}F]fluoro-5α-dihydrotestosterone
67-year-old man with CRPC and PSA of 789 ng/mL
FDHT-predominant nodal disease

Fox J, Schoder H, Larson S. **Molecular imaging of prostate cancer.** Current Opinion in Urology. 2012; 22:320-327.



16β-[^{18}F]fluoro-5α-dihydrotestosterone
69-year-old man with CRPC and PSA of 213 ng/mL
FDHT-predominant bone disease

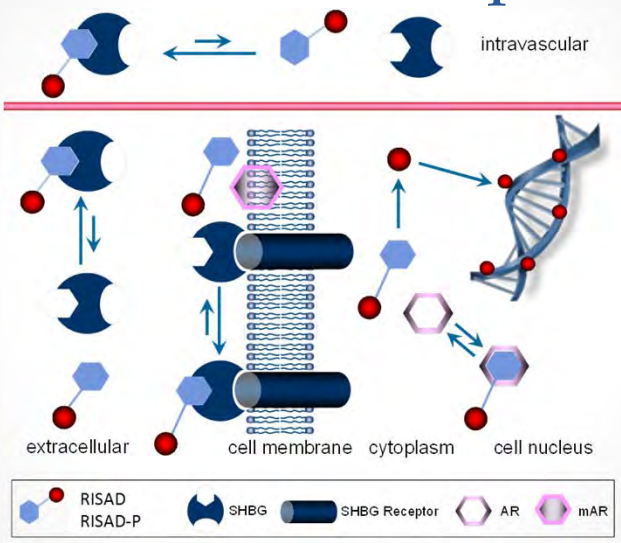
Fox J, Schoder H, Larson S. **Molecular imaging of prostate cancer.** Current Opinion in Urology. 2012; 22:320-327.

Why DNA targeted drug?

S-phase fraction is significantly higher in tumors with high AR density.

Recurrent prostate tumors with AR amplifications are highly proliferative.

Mechanism of uptake

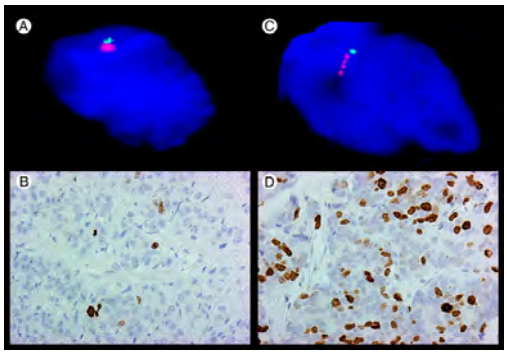


Kortylewicz ZP, Nearman J, Baranowska-Kortylewicz J. **Radiolabeled 5-iodo-3'-O-(17beta-succinyl-5alpha-androstan-3-one)-2'-deoxyuridine and its 5'-monophosphate for imaging and therapy of androgen receptor-positive cancers: synthesis and biological evaluation.** J Med Chem. 2009; 52:5124-43

AR and proliferation in PCa

AR NOT amplified **AR amplified**

FISH
one copy of chromosome X: cyan and AR gene: **purple**



FISH
one copy of chromosome X cyan with multiple copies of AR gene **purple**

Ki-67
only a few positive cells are present

Ki67
AR amplification is associated with high Ki-67 labeling index

- the higher the levels of AR in the tumor, the higher the proliferative activity
- biopsies from 475 patients

Haapala K, Kuukasjärvi T, Hyytinen E, Rantala I, Helin HJ, Koivisto PA. **Androgen receptor amplification is associated with increased cell proliferation in prostate cancer.** Human Pathol. 2007; 38:474 – 478.

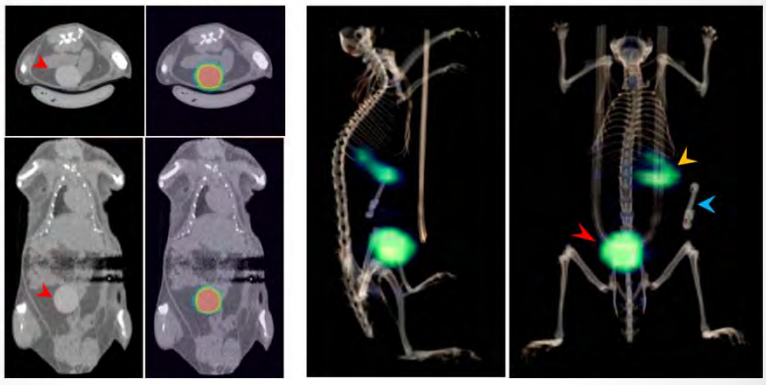
Li R, Wheeler T, Dai H, Frolov A, Thompson T, Ayala G. **High level of androgen receptor is associated with aggressive clinicopathologic features and decreased biochemical recurrence-free survival in prostate: cancer patients treated with radical prostatectomy.** Am J Surg Pathol. 2004 Jul;28(7):928-34.

^{125}IRISAD-P SPECT-CT

CT fused SPECT

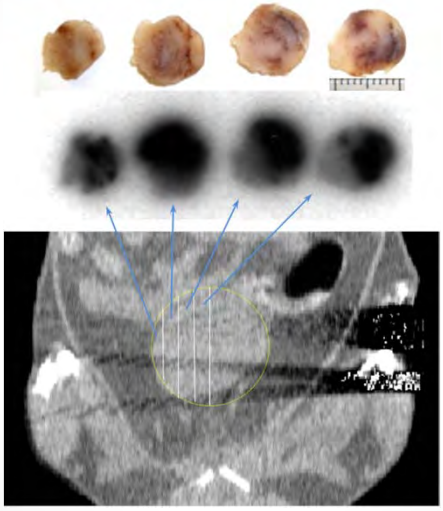
transverse

coronal



arrowheads: red – prostate cancer; yellow – stomach content; blue – ID transponder

^{125}IRISAD-P necropsy



Folate receptor

good target for MRT

Folate receptors are overexpressed by:

- ovarian cancer
- breast cancer
- colon cancer
- lung cancer
- prostate cancer
- nose and throat cancers
- brain tumors

Folate receptors are also overexpressed on hematopoietic malignancies of myeloid origin, including chronic and acute myelogenous leukemia.

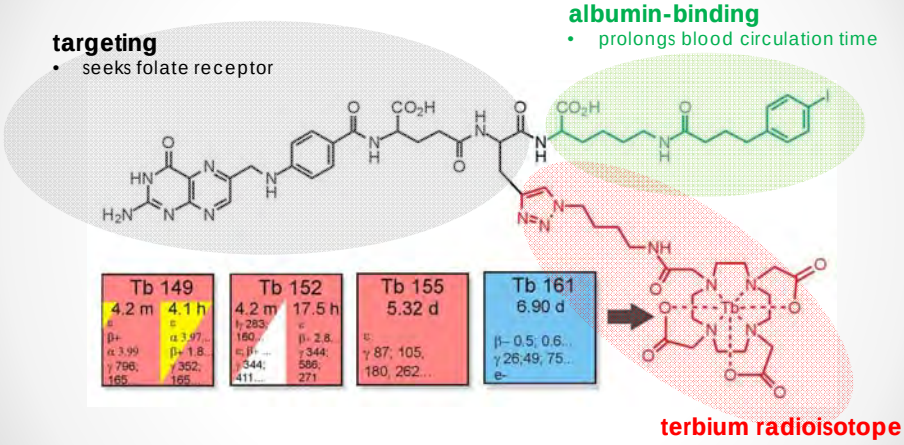
Folate receptor TMRT

http://medicalxpress.com/news/2012-12-terbium-swiss-army-knife-cancer.html

Folate receptor TMRT

targeting
- seeks folate receptor

albumin-binding
- prolongs blood circulation time



terbium radioisotope

Müller C, *et al*. A unique matched quadruplet of terbium radioisotopes for PET and SPECT and for α- and β- radionuclide therapy: an in vivo proof-of-concept study with a new receptor-targeted folate derivative. J Nucl Med. 2012; 53:1951-9.

NETs peptides

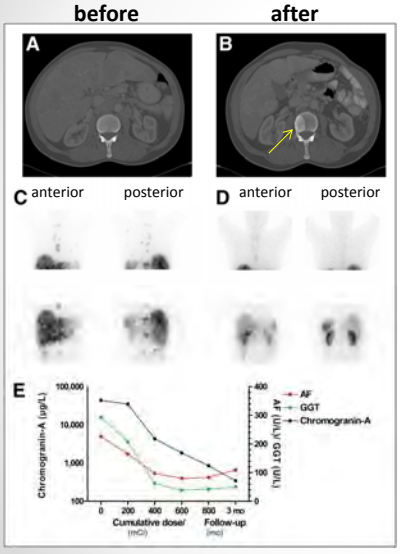
NET peptides

Peptide	hSSTR1	hSSTR2	hSSTR3	hSSTR4	hSSTR5
^{111}In-octreotide	>10,000	22±3.6	182±13	>1,000	237±52
^{90}Y- DOTATOC	>10,000	11±1.7	389±135	>10,000	114±29
^{90}Y-DOTALAN	>10,000	23±5	290±105	>10,000	16±3.4
^{90}Y-DOTA-OC	>10,000	20±2	27±8	>10,000	57±22
^{111}In-DTPA-Tyr3-octreotate	>10,000	1.3±0.2	>10,000	433±16	>1,000
^{90}Y-DOTA-Tyr3-octreotate	>10,000	1.6±0.4	>1,000	523±239	187±50

Affinity profiles (IC_{50})a for human somatostatin receptors SSTR1–SSTR5 (hSSTR1–hSSTR5) of a series of somatostatin analogues.

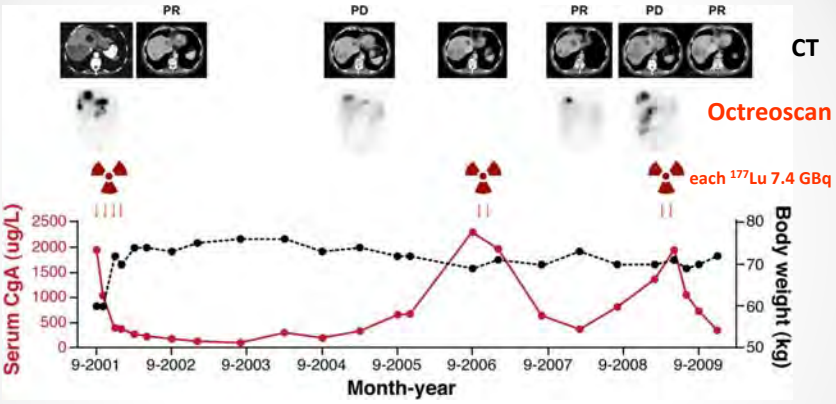
All values are IC_{50}±SEM in nM.

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate



Patient with a NET of unknown origin with multiple liver and bone metastases
Treatment: 1 GBq of ^{177}Lu-octreotate.
A. CT before treatment with ^{177}Lu-octreotate, with no evidence of bone metastases.
B. CT 6 wk after treatment with ^{177}Lu-octreotate, showing bone metastasis located at L2 and shrinkage (pseudocirrhosis) of liver.
C. [^{111}In-DTPA^{0}]octreotide scintigraphy before treatment with ^{177}Lu-octreotate showing uptake in multiple liver and bone metastases.
D. [^{111}In-DTPA^{0}]octreotide scintigraphy 4 months after last treatment with ^{177}Lu-octreotate, showing reduction of liver and bone metastases and shrinkage of liver.
E. Serum alkaline phosphatase, γ-glutamyl transpeptidase, and chromogranin A levels during and 3 months after treatment.

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate



Patient with gastro-entero-pancreatic neuroendocrine tumor.

Plot shows serum chromogranin A concentrations (red symbols, closed line) and patient's weight (black symbols, dotted line).

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

Patients: 76 patients with neuroendocrine gastro-entero-pancreatic tumors

Doses: 100 mCi were injected in 20 min; 150 and 200 mCi injected in 30 min

Interval between treatments: was 6–9 weeks

Cumulative dose: 750–800 mCi (27.8–29.6 GBq)

Complete remission: one patient

Partial remission 22 patients (29%),

Minor remission: 9 patients (12%)

Stable disease: 30 patients (40%)

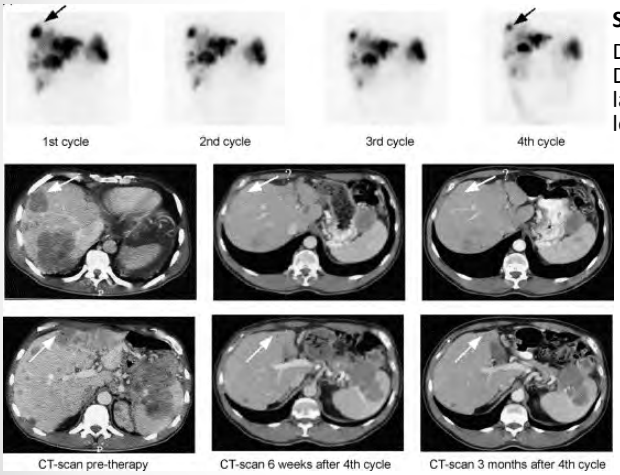
Progressive disease: 14 patients (18%)

Six out of 32 patients who had stable disease or tumor regression after the therapy and were also evaluated after 12 months (mean 18 months from therapy start) developed progressive disease.

In the other 26, the tumor response was unchanged.

Median time to progression was not reached at 25 months from the beginning of therapy.

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate



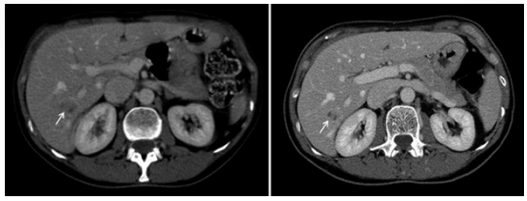
Scintigraphy after each cycle

Decreased uptake of [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate on the last scan; black arrows = index lesion

At 3 and 6 months after four cycles of therapy, the patient had a partial remission (>50% decrease in tumor volume on CT); white arrows = index lesion

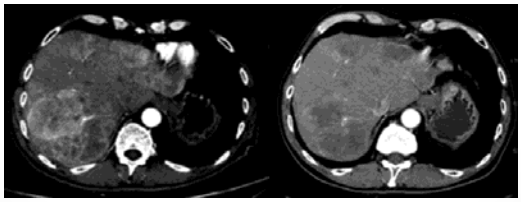
- Teunissen et al. Peptide receptor radionuclide therapy. Best Practice & Res Clinic Gastroenter. 2005; 19:595-616.

[^{90}Y-DOTA-D-Phe^{1}-Tyr^{3}]octreotide



pre-treatment CT
liver metastasis 33 mm

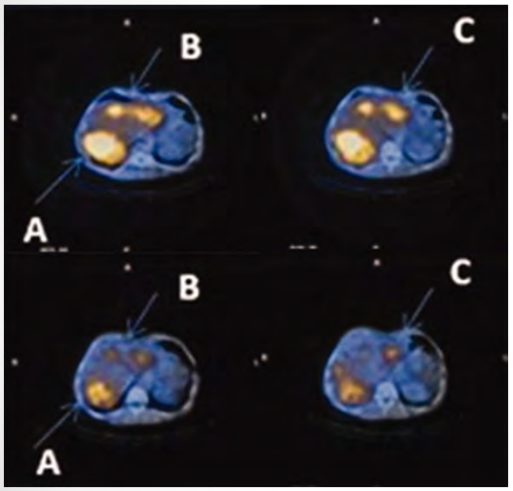
post-treatment CT



contrast enhanced

- **Cancer**
  Volume 118, Issue 11, pages 2915-2924, 21 OCT 2011 DOI: 10.1002/cncr.26616
  http://onlinelibrary.wiley.com/doi/10.1002/cncr.26616/full#fig1

^{90}Y-DOTA-D-Phe1-Tyr3 octreotide



1st cycle

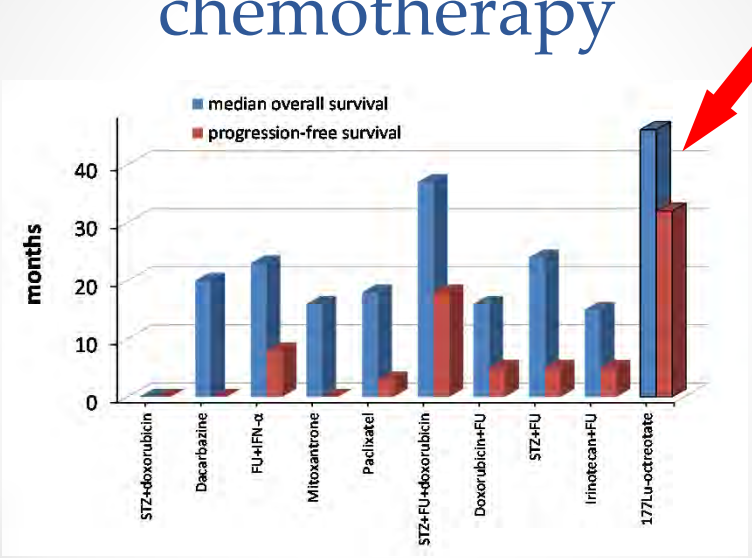
2nd cycle

SPECT Images

Letters A through C mark metastases

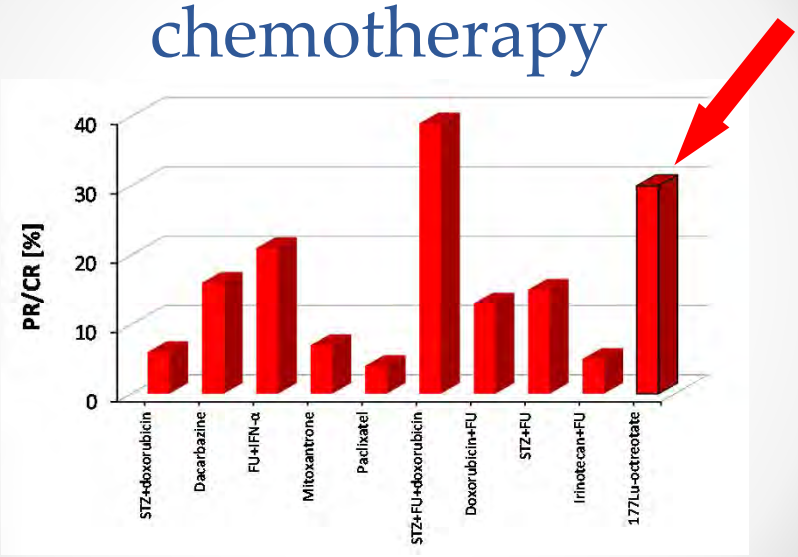
Cancer
Volume 118, Issue 11, pages 2915-2924, 21 OCT 2011 DOI: 10.1002/cncr.26616
http://onlinelibrary.wiley.com/doi/10.1002/cncr.26616/full#fig3

^{177}Lu-Octreotate vs chemotherapy



Kwekkeboom *et al.* Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008 May 1;26(13):2124-30. doi: 10.1200/JCO.2007.15.2553.

177Lu-Octreotate vs chemotherapy



Kwekkeboom *et al.* Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008 May 1;26(13):2124-30. doi: 10.1200/JCO.2007.15.2553.

In conclusion…

- targeted molecular radiotherapy eradicates cancer cells by targeting specific receptors or antigens, e.g., Bexxar or Zevalin, or physiological processes, e.g., Xofigo (formerly alpharadin)
- typically, the design of targeting moieties allows the incorporation of imaging radionuclides for PET or SPECT as well as therapeutic radionuclides for molecular radiotherapy (theranostic approach)
- most molecular radiotherapeutics allow for the adoptive approach

Co-investigators

Charles A. Enke, M.D.
Elizabeth Mack, M.Sc.
Michio Abe, M.D., Ph.D.
Jessica Nearman, B.Sc.
Kathy Estes, Ph.D.
Zbigniew P. Kortylewicz, Ph.D.
Guang Han, M.D., Ph.D.
Yu Kimura, M.D., Ph.D.
R. Lee Mosley, Ph.D.
Kotaro Inoue, M.D., Ph.D.

Funding

W81XWH-04-1-0463
DAMD17-99-1-9313
POC grant Central Administration
UNeMed
Bayer Schering Pharma G4T Program
2P41RR000954
OC030177