Current practice of Therapeutic Nuclear Medicine in Oncology

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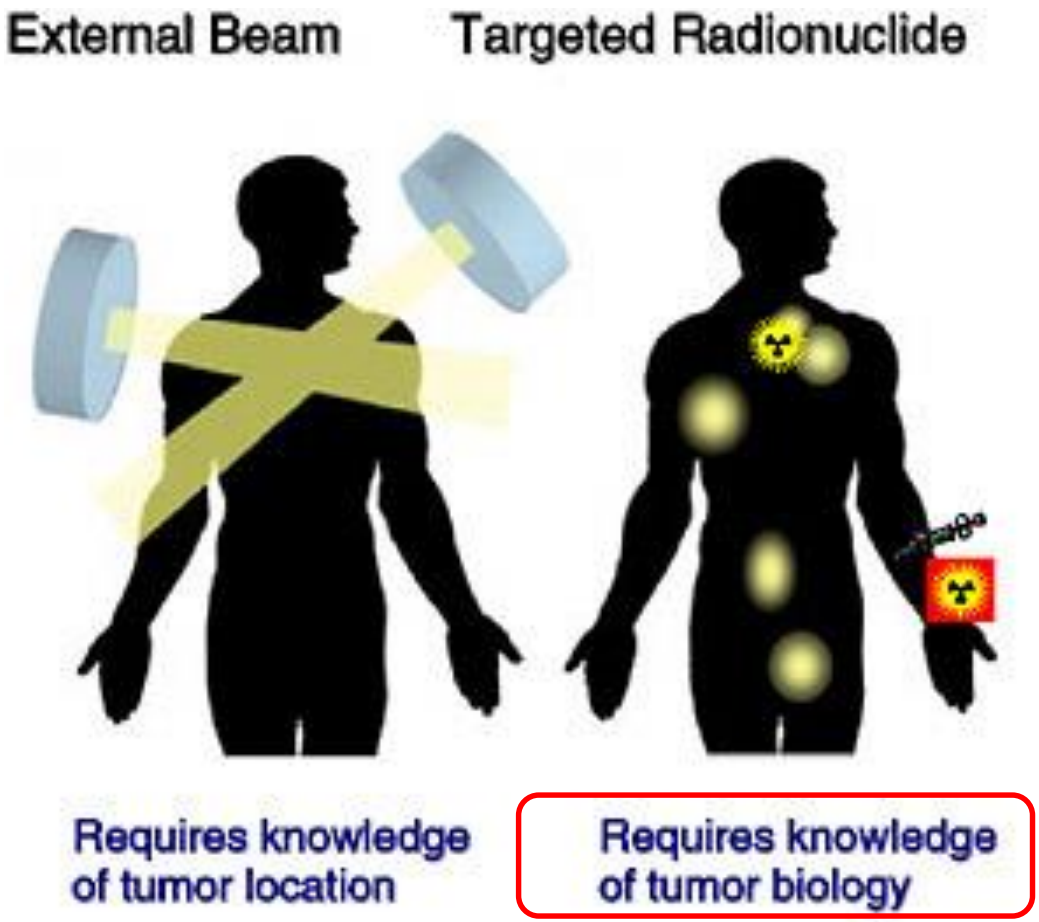
2018/11/18

Radionuclide therapy



SOURCE: Courtesy of Michael Zalutsky, Duke University

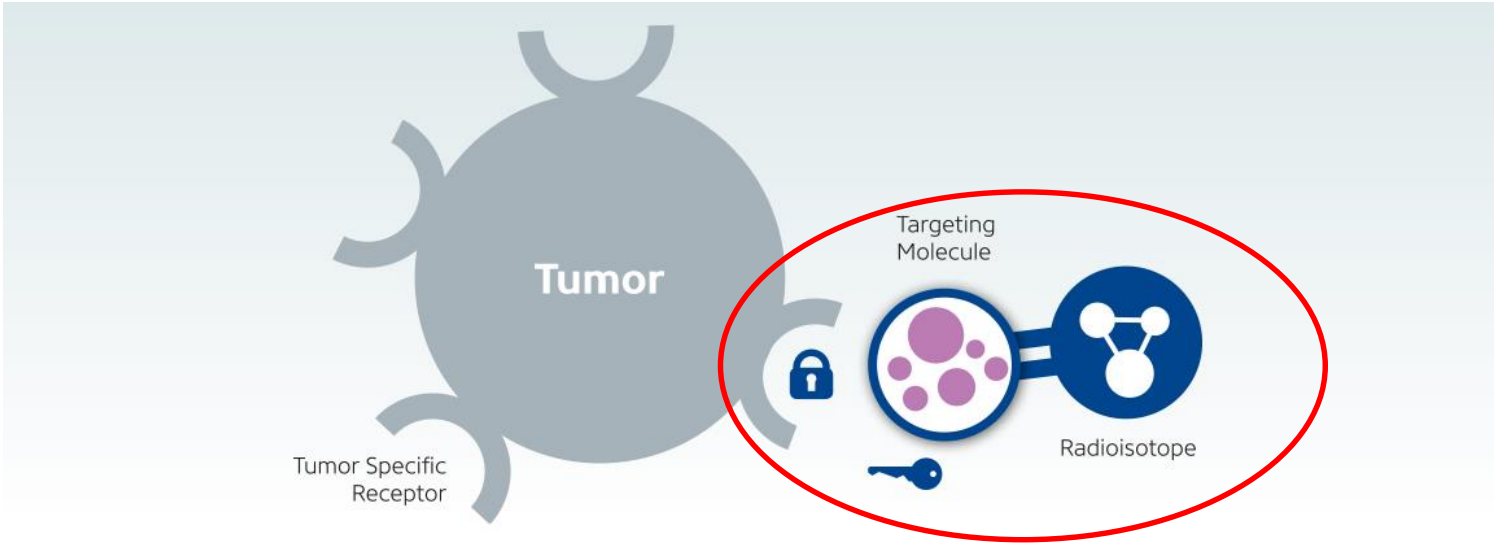
Types of radionuclide therapy

- Targeted radionuclide therapy (TRNT)
- Interventional approach
  - Selective intra-arterial radionuclide therapy (SIRT)
    - Hepatic malignancies, salvage setting
      - TheraSpheres, SIR-spheres (Yttrium-90 microspheres), I-131-lipiodal
    - Interventional radiologist
  - I-125 seeds implantation
    - Radiation oncologist

Targeted radionuclide therapy (TRNT)

- High-affinity molecules + radionuclides

  ➔ target molecule on the surface of tumor cells

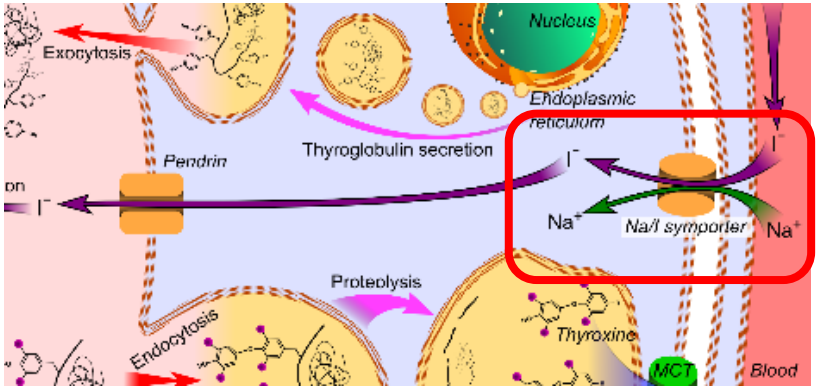


Applications

- Thyroid cancer
- Painful bone metastases
- Non-Hodgkin lymphoma
- Prostate cancer
- Neuroendocrine tumors

Thyroid cancer

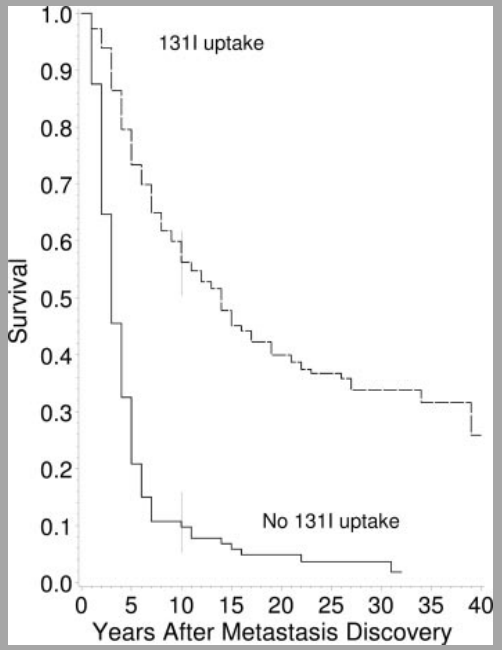
- Since 1940s
- Indication:
  - Ablation of thyroid residues after total thyroidectomy
  - Treatment of iodine-absorbing recurrences of metastases of DTC
  - Treatment of iodine-absorbing inoperable DTC



- Mechanism of uptake
  - Na/I symporter
- Absorbed dose
  - from <10 ~1000Gy
  - 40~300 Gy for remnants
  - 40~80 Gy for metastases

Benefit of RAI therapy in DTC

Long-Term Outcome of 444 Patients with Distant Metastases from Papillary and Follicular Thyroid Carcinoma: Benefits and Limits of Radioiodine Therapy
J Clin Endocrinol Metab, August 2006, 91(8):2892–2899



- Reduction of 10-year risk recurrence: 50%
- Decrease in mortality rate:
  - T > 1~1.5cm, muticentric, cervical LN mets, soft tissue invasion
  - Significant improved overall survival in stage II pts received RAI therapy (NTCTCSG data)
  - 43 % higher relative high risk of death in high-risk patients (stage III, IV) didn't receive RAI therapy (NTCTCSG data)

J Clin Endocrinol Metab 1990; 71:414
Am J Med 1994;97:418
J Clin Endocrinol Metab 2004 89:3668
Thyroid 2006; 16:1229

Case sharing

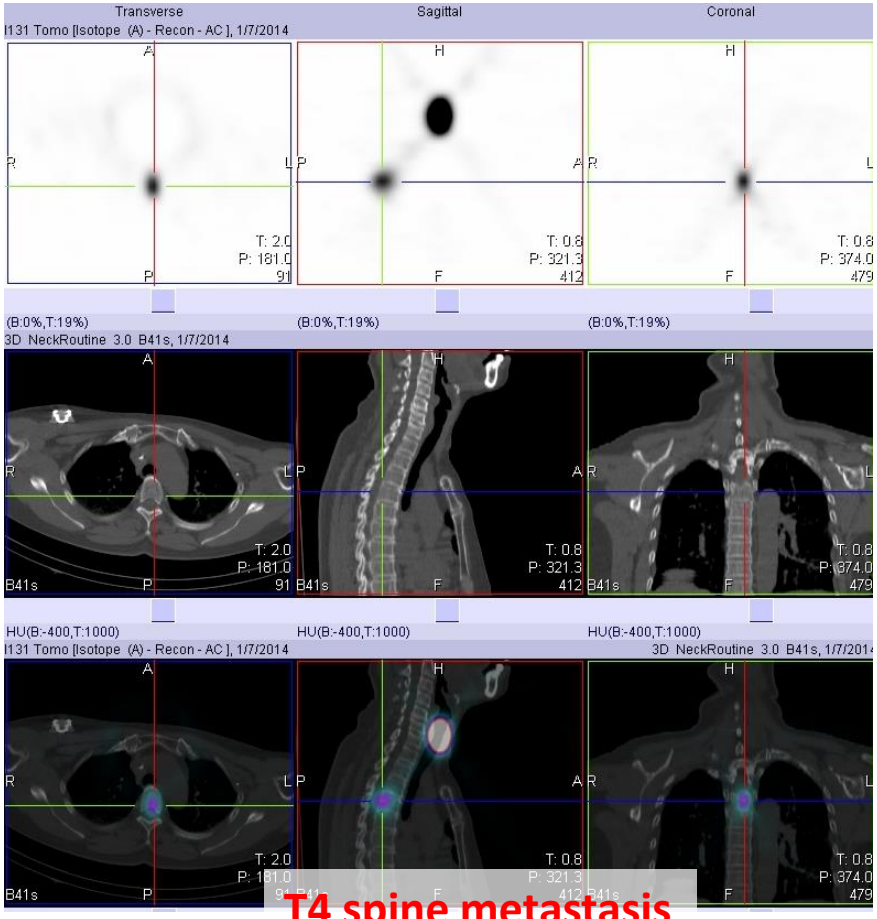
61y lady

- **Papillary carcinoma, follicular variant**

·Two tumors, up to 0.45x0.3 cm

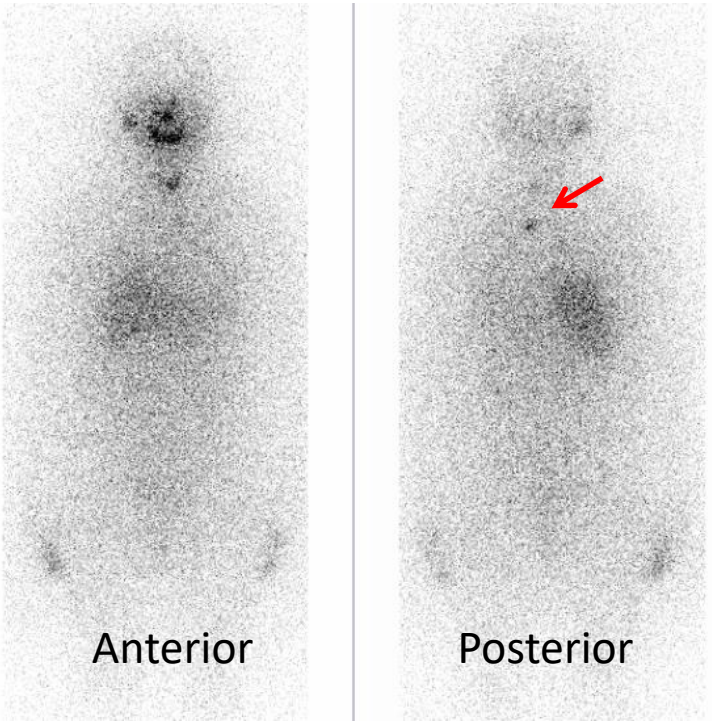
·No regional LN metastasis (0/1)

Low risk

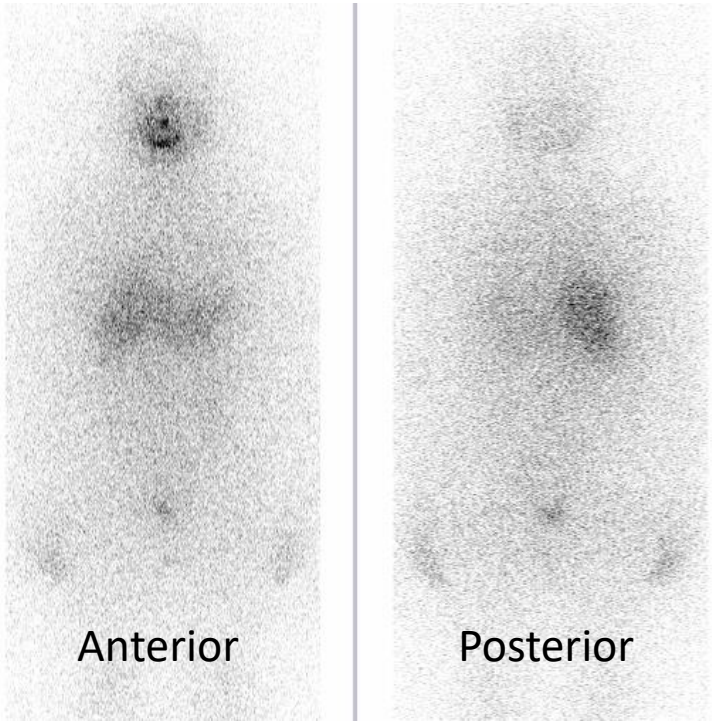


T4 spine metastasis

200mCi (2014/8)



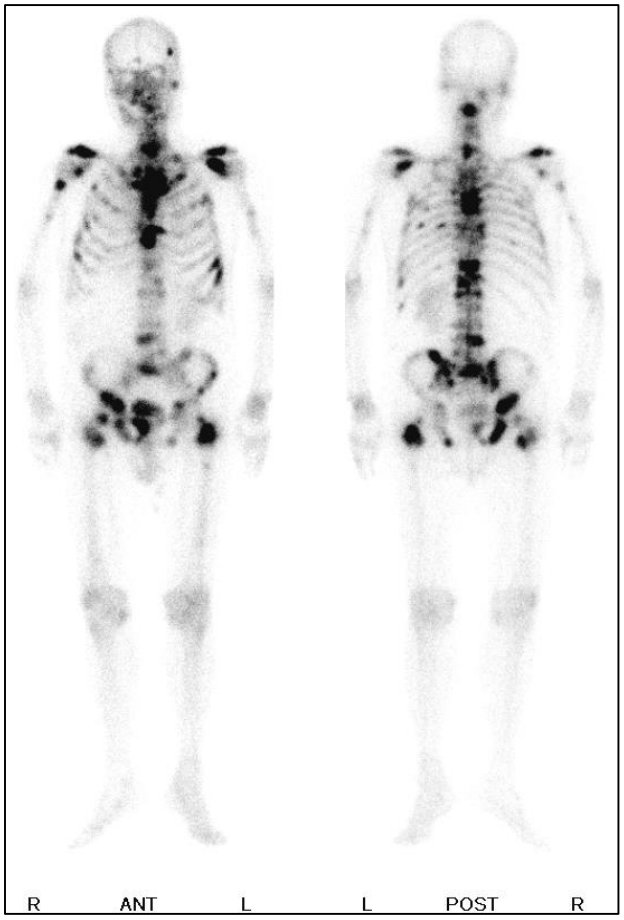
200mCi (2015/10)



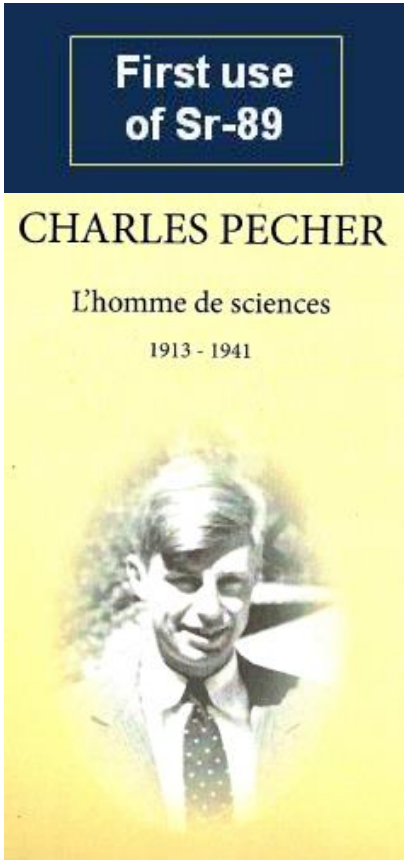
Suppressed Tg: <0.04

2018/7➔ Stimulated Tg: <0.04

PAIN



- Sr-89-chloride, since 1940s
  - Group II metal, act like calcium
  - β emitter: 1.46MeV (maximum), 0.58MeV(mean)
  - Physical half-life: 50.5 days
  - Activity: 1.5~2.2 MBq/kg



Palliation for painful bone metastases

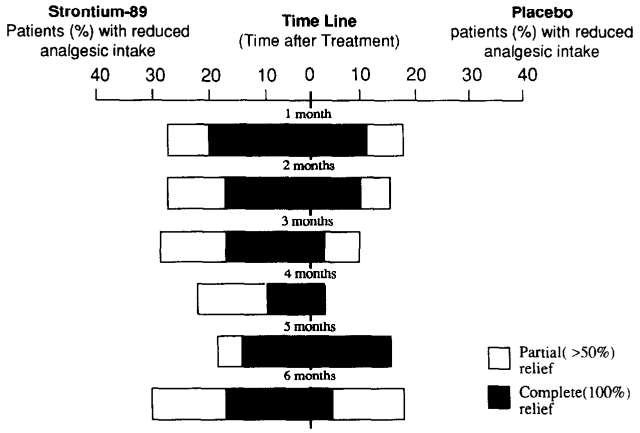
- Strontium(Sr)-89-chloride
  - Group II metal, act like calcium

- Bisphosphonates, high affinity for hydroxyapatite in bone
  - Samarium(Sm)-153-EDTMP (Qudramet, Sm-153 lexidronam)
  - Rhenium-186 HEDP (Re-186 Etidronate)
  - Rhenium-188 HEDP

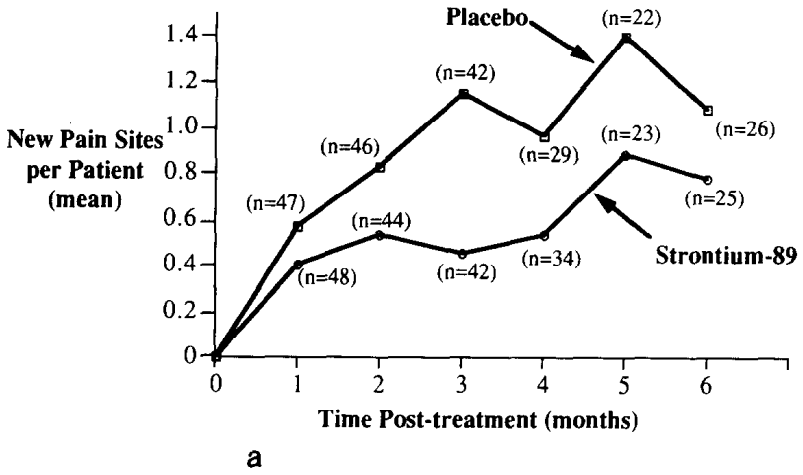
US FDA approval in 1993

First use of Sr-89

Reduced analgesic use



Less new pain sites



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Less needs of EBRT

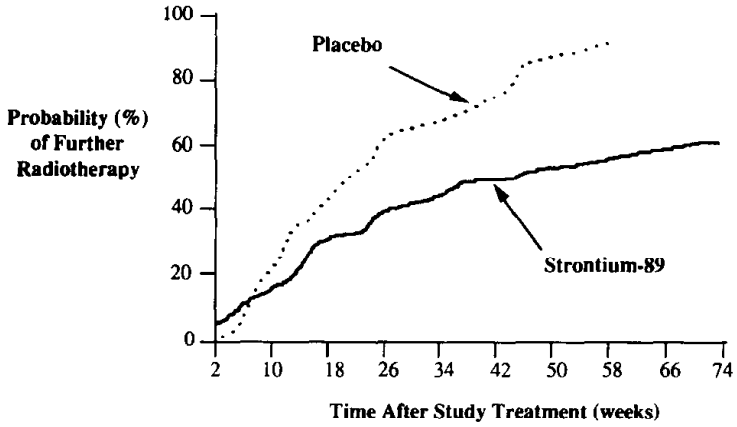


Table 2. Hematology toxicity

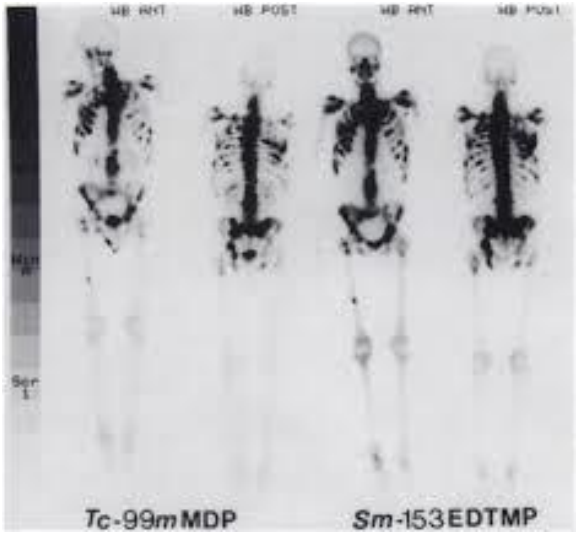
	Number of patients (%)	
	Strontium-89	Placebo
Hematologic events: up to 6 months post-treatment		
Hemorrhage	10 (14.9%)	3 (5.2%)
Infection	9 (13.4%)	7 (12.1%)
Receipt of platelets	5 (7.46%)	0
Receipt of other blood products	26 (38.8%)	24 (41.4%)

Dosing vs. side effects

ELEMENTS → CHEMICAL COMPOUNDS

Bisphosphonates

- Sm-153-EDTMP (FDA approval, 1997)
  - Bisphosphonate EDTMP
  - β emitter: 0.81MeV (maximum), 0.23MeV(mean)
  - γ emission: 103 KeV (28% abundance)
    - Physical half-life: 1.9 days
    - Activity: 37 MBq/kg
    - Target dose: 3~60 Gy (222 MBq/kg)

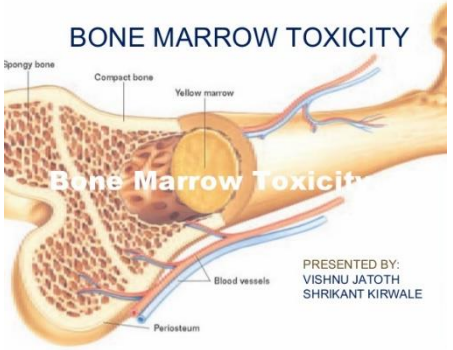


Sr-89 vs. Sm-153

Radiopharmaceutical	Physical $t_{1/2}$ (d)	Average particle energy (MeV) per decay	Range in tissue (mm)	Bone surface to red bone marrow dose ratio
Metastron ($^{89}SrCl_2$)	50.5	0.58	2.4	1.6*
Quadramet (^{153}Sm-EDTMP)	1.9	0.22	0.55	4.4†

Clin Cancer Res 2006;12(20 Suppl) October 15, 2006

- Sm-153-EDTMP has
  - Shorter half-life
  - Shorter tissue penetration range
  - Better targeting dose ratio
- For palliative setting

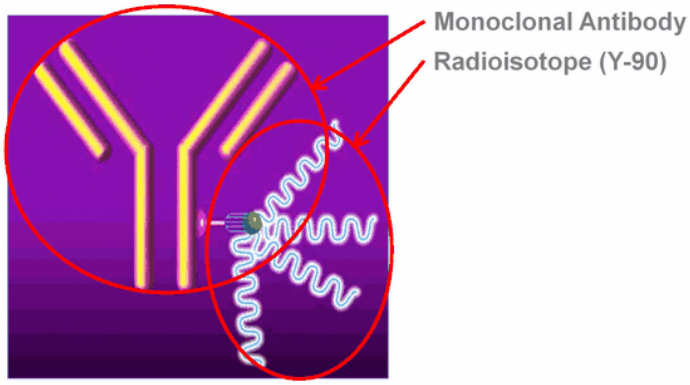


ANTIGENS

Radioimmunotherapy

Non-Hodgkin lymphoma

- Zevalin® (Ibritumomab tiuxetan) (2002, U.S. FDA approval)
  - First radioimmunotherapy
    - Recurrent and resistant forms of low-grade follicular B-cell non-Hodgkin's lymphoma.
  - CD20 and 90Y were used as an antigen and a radionuclide
  - 8-y PFS: 41% vs. 22%(control group)



- Bexxar
  - CD20 and I-131
  - CHOP-R and CHOP-RIT
    - 2-year PFS: 76% vs. 80%
    - 2-year estimate OS: 97% vs. 93%
  - Withdrawn from the market in October 2013

- Lymphocide® (Epratuzumab)
  - CD22 and 90Y
  - phase III of clinical trials
- Theragyn (Pemtumomab)
  - Monoclonal mouse antibody against mucin MUC1 and Y-90.
  - phase III of clinical trials
- And more …

α THERAPY & OVERALL SURVIVAL BENEFIT

New milestones 2013

The NEW ENGLAND JOURNAL of MEDICINE

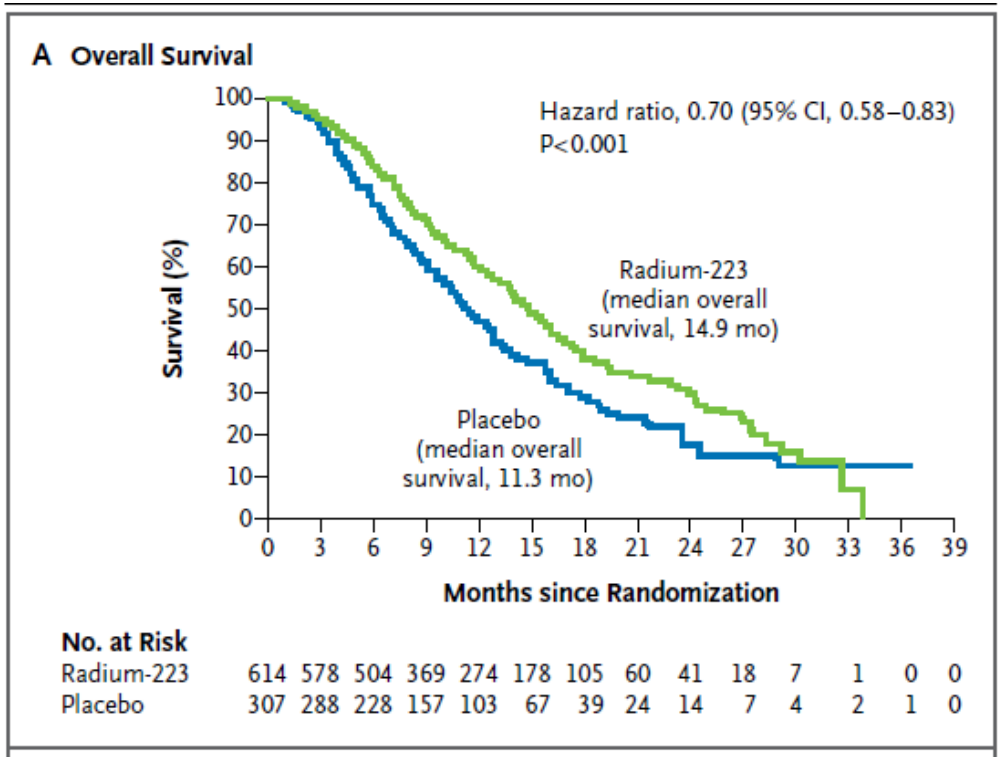
ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fossâ, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

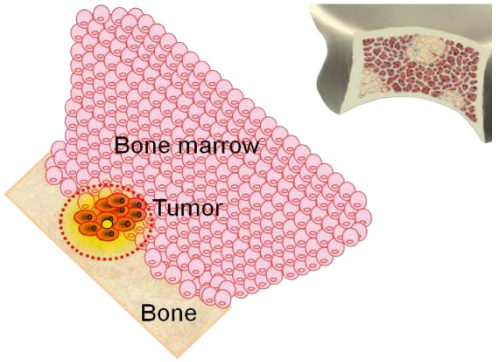
Overall Survival benefit:

ALSYMPCA: 14.9 vs. 11.2 mo



Prostate cancer, mCRPC

- Radium(Ra)-223 chloride (Xofigo)
  - Group II metal, act like calcium
    - Physical half-life: 11.4 days
  - **α emitter**: 5.6~74 MeV, short range < 100um
  - Activity: 55 kBq/kg, 4-week interval *6
  - Absorbed dose to metastases
    - 0.2~1.9 Gy
- Side effect:
  - tolerable marrow toxicity and GI disturbs



Notice

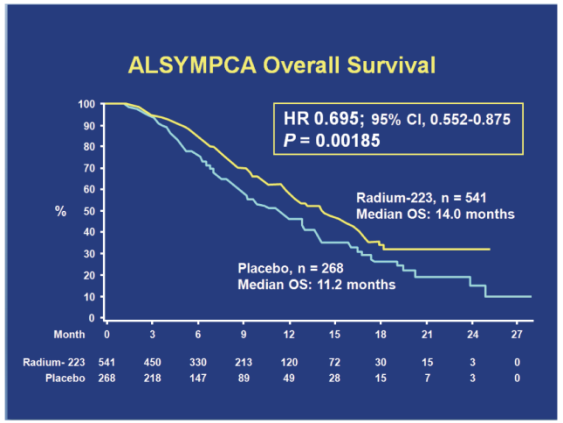
- Abiraterone combination with Xofigo
  - Died on average 2.6 months earlier vs. placebo arm
  - Fractures: 29% vs. 11% of placebo combination
- Recommendation (EMA)
  - Monotherapy or in combination with an LHRH analogue
  - Symptomatic bone metastases and no known visceral metastases
  - Progression after >2 prior lines of systemic therapy
  - Ineligible for any available systemic mCRPC treatment.

Radium-223 (Alpharadin)

A Novel Targeted Alpha-Emitter for Bone-Metastatic Castrate-Resistant Prostate Cancer

OLIVER SARTOR, M.D.

North American Principal Investigator, ALSYMPCA trial
Laborde Professor of Cancer Research
Tulane Cancer Center,
Tulane University School of Medicine
New Orleans, LA



More than 900 patients were enrolled in the ALSYMPCA trial, but an early "interim" analysis was performed to ensure that safety and ethical issues were appropriate for trial continuation.

Surprisingly, this interim analysis (performed after 314 deaths) demonstrated a strong and positive survival advantage for those treated with the radium-223. In the interim analysis, patients in the placebo group lived a median of 11.2 months, while the patients in the radium-223 group lived a median of 14.0 months (5). Please note that this trial, along with every other trial has considerable heterogeneity around the median. This compares favorably with other trials performed predominantly in patients previously treated with docetaxel (3,4). The probability of this result being due to chance was less than 2 in 1,000. A final analysis has recently been reported with more follow-up: The median survivals improved with the placebo group living a median of 11.3 months and the radium-223 group treated a median of 14.9 months (8).

The positive survival results led to the trial being stopped at the interim analysis. It was considered unethical to

Treatment options for mCRPC

- Chemotherapy: Docetaxel & Cabazitaxel
  - 2.5-mo Docetaxel vs. mitoxantrone (16.4 vs. 18.9; 2004)
  - 2.4-mo Cabazitaxel vs. mitoxantrone (15.1 vs. 12.7, post-docetaxel setting; 2010)
- Autologous cellular immunotherapy: Sipuleucel-T
  - 4.1-mo vs. placebo (25.8 vs. 21.7; 2010)
- 2nd generation hormonal therapy: Abiraterone & Enzalutamide
  - 4.6-mo and 4.4-mo Abiraterone vs. placebo (15.8 vs. 11.2, post-docetaxel setting; 34.7 vs. 30.3, docetaxel naïve; 2012&2015)
  - 2.2-mo Enzalutamide vs. placebo (32.4 vs. 30.2; 2014)
- Bone targeting therapy
  - 3.8-mo Ra-223 vs. placebo (14.9 vs. 11.3; 2013)

PEPTIDE RECEPTORS

PRRT

Neuroendocrine tumors

- LUTATHERA(177Lu-DOTA-Tyr3-Octreotate)
  - Approved by U.S. FDA in Jan. 2018

Peptide receptor radionuclide therapy (**PRRT**)

- 177Lu-DOTA-Tyr3-Octreotate
  - A somatostatin analogue peptide
  - Somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (NETTER-1 study)
    - 79% reduction in risk of disease progression or death vs. Octreotide arm
    - PFS: Lutathera arm not been reached vs. 8.4 mo
    - CR and PR: 13% vs. 4%

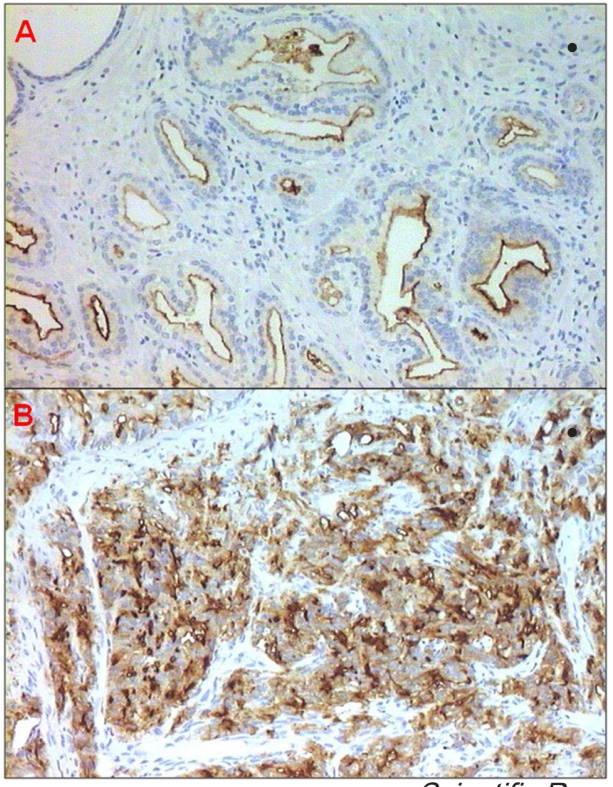
Who’s the next rising star ?

Prostate-specific membrane antigen (PSMA)

Type 2 integral membrane, expressed on the apical surface of endothelial cells

PSMA

- Integral membrane protein
- Several enzymatic functions
- Upregulated with androgen deprivation
- RT-PCR used to detect in serum; not verified as screening tool/ marker
- Expression correlates with cancer aggressiveness and represents an independent indicator of poor prognosis

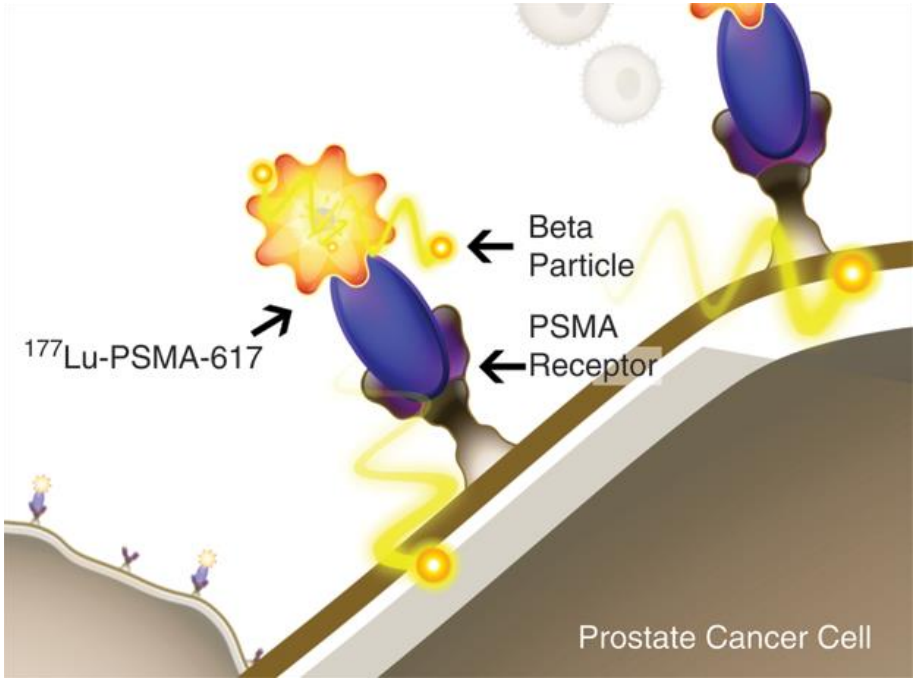


(**A**) GS 6 (3 + 3, Grade Group 1) prostate adenocarcinoma (10 × magnification) with moderate endoluminal membrane staining.

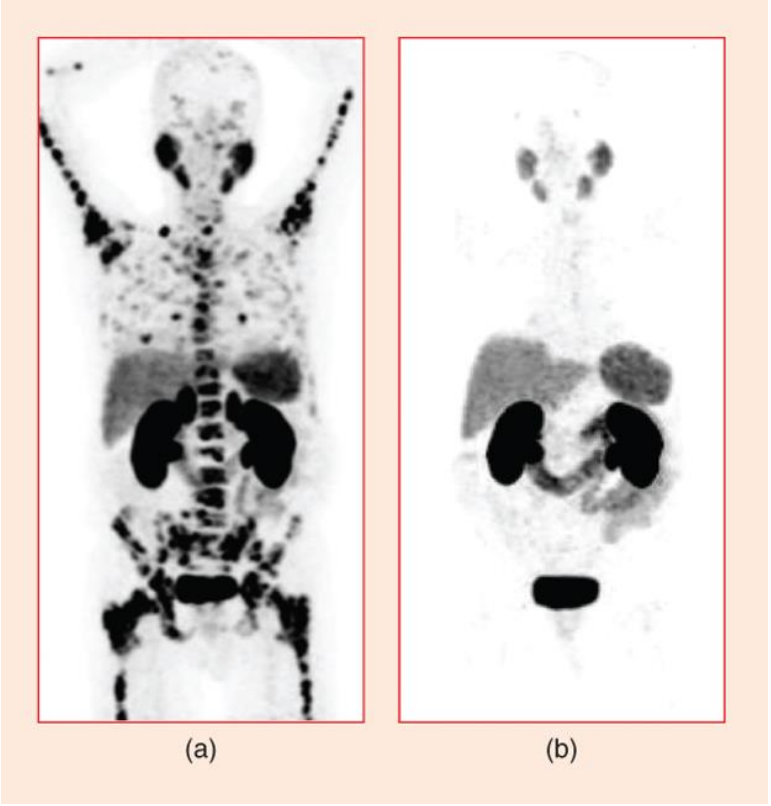
(**B**) GS 8 (4 + 4, Grade Group 4) prostate adenocarcinoma (10 × magnification) with strong membrane staining

Scientific Reports **volume 8**, Article number: 4254 (2018)

Phase 3 clinical trial in recruiting



(Image courtesy of Endocyte, Inc.)

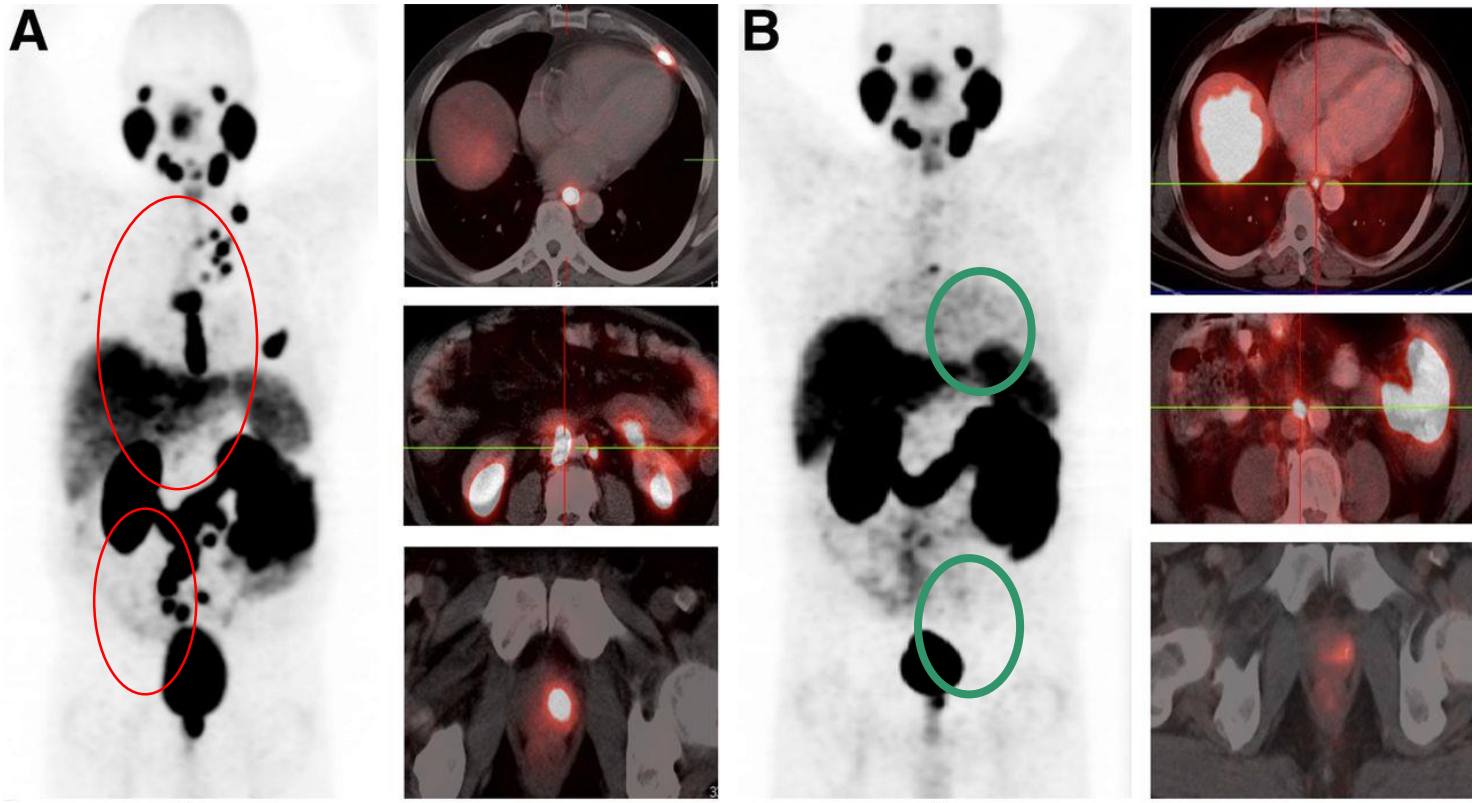


Prior researches

- **German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients** (J Nucl Med 2017; 58:85–90)
  - 145 patients, follow-up time (16 weeks), retrospective
  - 45% of the patients exhibited a decrease of ≥50% in PSA levels.
    - The response was early in over 40% of the patients, usually after the first course

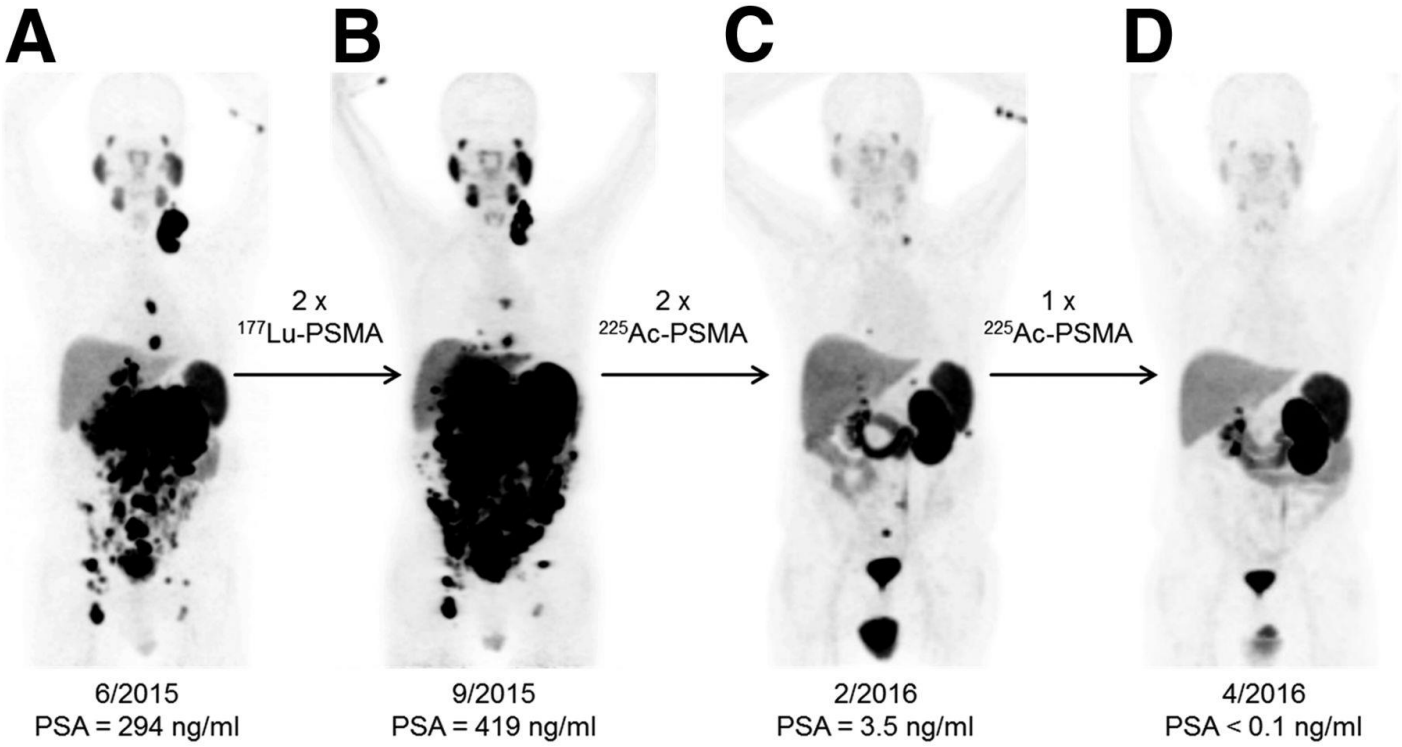
- **[^{177}Lu]-PSMA-617 radionuclide treatment in patients with mCRPC(LuPSMA trial): a single-centre, single-arm, phase 2 study** (Lancet oncol 2018;19:725-726)
  - 30 patients (mean activity: 7.5 GBq per cycle)
  - 17 (57%) ➔ PSA decline > 50%
  - 82% (14/17 measurable disease) ➔ objective response in nodal or visceral disease
  - Most common toxicity
    - grade 1 dry mouth: 26 (87%)
    - grade 1 and 2 transient nausea in 15 (50%), G1-2 fatigue in 15 (50%), Grade 3 or 4 thrombocytopenia in 4(13%)
    - No treatment-related deaths.

177Lu-PSMA-I&T



PET/CT in patient 3. Martina Weineisen et al. J Nucl Med 2015;56:1169-1176

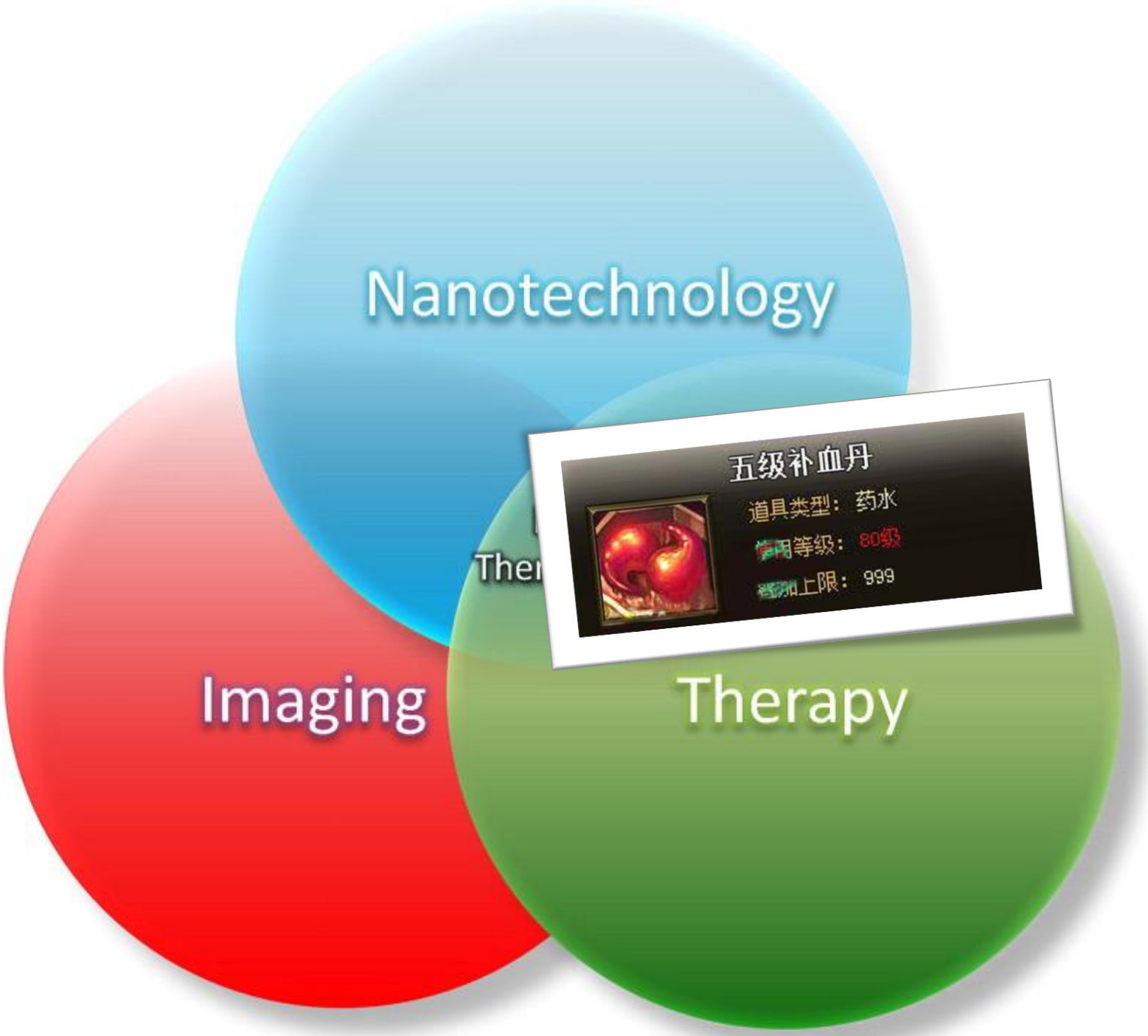
α PSMA therapy



J Nucl Med 2016; 57:1941–1944

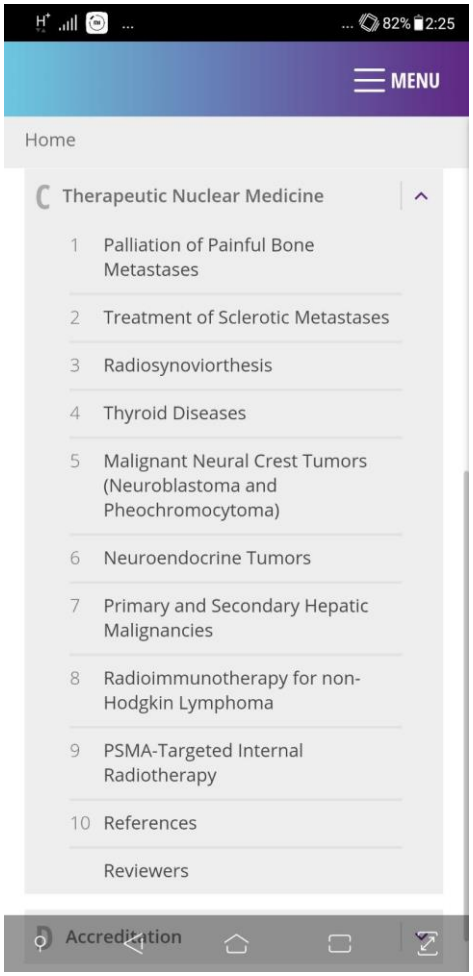
Hurdles

- Overall survival benefit
  - I-131 therapy for thyroid cancer is too ancient to have prospective randomized controlled trial
  - Difficult to translate Ra-223 OS benefit in mCRPC into the clinical practice
- Dosimetry
  - Dose-response correlation ➔ optimum result not reached
- Radiation regulation/ safety
  - Need extra effort and may let to hesitation of the clinicians
  - Nuclear medicine physicians should be helpful
- Price
  - Too high, if it's out of pocket


Nanotechnology
Imaging
Therapy
五级补血丹
道具类型：药水
等级：80级
上限：999

Conclusion

- I-131 therapy is a standard treatment of DTC
- Ra-223 therapy for symptomatic mCRPC prolongs overall survival
- Lu-177-oxodotreotide showed PFS benefit in somatostatin receptor positive gastroenteropancreatic NETs
- PSMA PRLT has a GREAT chance to improve the outcome of prostate cancer
- More radionuclide therapies is on the way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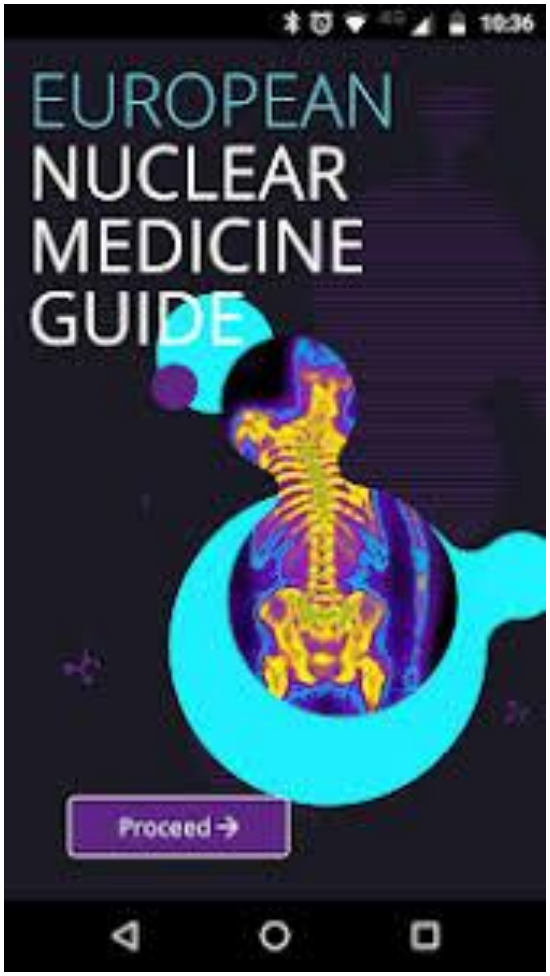
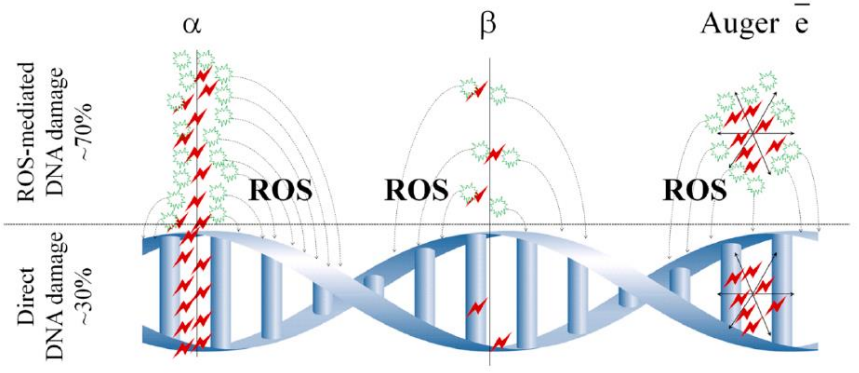
MENU
Home
Therapeutic Nuclear Medicine
1 Palliation of Painful Bone Metastases
2 Treatment of Sclerotic Metastases
3 Radiosynoviorthesis
4 Thyroid Diseases
5 Malignant Neural Crest Tumors (Neuroblastoma and Pheochromocytoma)
6 Neuroendocrine Tumors
7 Primary and Secondary Hepatic Malignancies
8 Radioimmunotherapy for non-Hodgkin Lymphoma
9 PSMA-Targeted Internal Radiotherapy
10 References
Reviewers
Accreditation


Thank you


10:36
EUROPEAN
NUCLEAR
MEDICINE
GUIDE
Proceed

DNA damage from radionuclide

- Linear energy transfer (LET)
  - α-emitters: ~80 keV/um
  - β-emitters: ~0.2-2.0 keV/um
  - Auger electron: 4-26 keV/um
- Optimum half-life for radionuclide therapy
  - 6 h~ 7d



ROS: reactive oxygen species

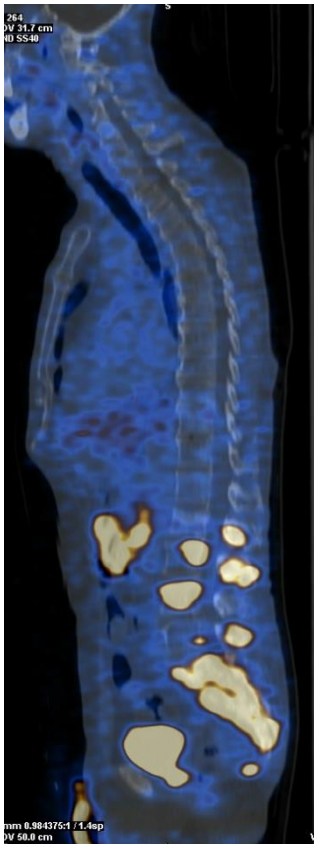
Int. J. Mol. Sci. **2016**, *17*, 33; doi:10.3390/ijms17010033

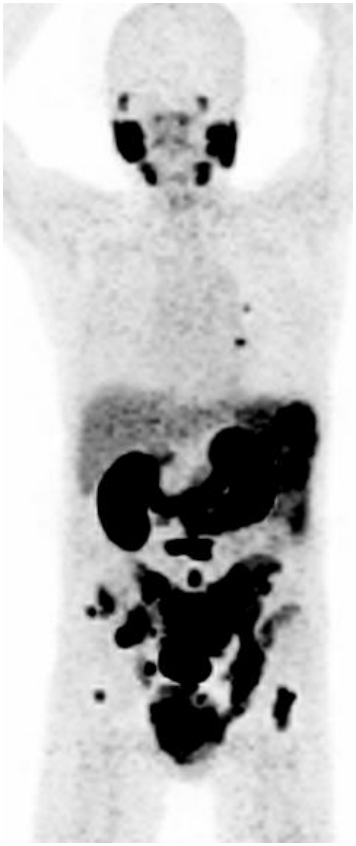
Theranostic

SATHEKGE, M. Targeted radionuclide therapy. **Continuing Medical Education**, [S.l.], v. 31, n. 8, p. 289-294, aug. 2013. ISSN 2078-5143.

Selective intra-arterial radionuclide therapy (SIRT)

- Hepatic malignancies, salvage setting
  - Y-90 microspheres
    - β emitter: 2.2MeV (maximum
    - Physical half-life: 2.67 days
    - TheraSpheres
      - approved by the Food and Drug Administration (FDA) in 1999 for the treatment of unresectable HCC
    - SIR-spheres (Yttrium-90 microspheres)
      - approved by the US FDA in 2002 for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).
      - Target dose: ~1000 Gy
  - I-131-lipiodal
    - Target dose: 43 ±22 mGy/MBq





Ga-68-PSMA PET/CT scan & Lu-177 PSMA therapy

Radionuclide	$T_{1/2}$, h	E_{max}, MeV (*)	Method of Producing
^{124}I	100.1	β − 1.6 (~90%); 2.2 (~10%)	cyclotron
^{131}I	192.0	β − 0.7 (89%); γ − 0.4 (82%); β/γ ** = 1	nuclear reactor
^{86}Y	14.7	β − 1.2 (~90%); 1.6 (~10%)	cyclotron
^{90}Y	64.8	β − 2.2 (100%)	generator $^{90}Sr \rightarrow {}^{90}Y$
^{177}Lu	160.8	β − 0.5 (100%)	nuclear reactor
^{188}Re	17.0	β − 2.0 (100%)	generator $^{188}W \rightarrow {}^{188}Re$
^{64}Cu	12.7	β − 0.65 (61.5%), β − 0.58 (38.5%)	Cyclotron
^{67}Cu	61.9	β − 0.4 (100%)	cyclotron
^{89}Zr	78.0	B ± 0.9 (100%)	cyclotron
^{212}Pb	10.6	β − 0.6 (~80%); γ − 0.2 (44%); 0.08 (18%)	generator $^{228}Th \rightarrow {}^{220}Rn \rightarrow {}^{216}Po \rightarrow {}^{212}Pb$
^{212}Bi	1.0	α − 6.0 (100%); β − 2.0 (100%); α/β ** = 0.67	generator $^{228}Th \rightarrow {}^{224}Ra \rightarrow {}^{212}Bi$
^{213}Bi	0.7	α − 5.8 (97%); β − 1.4 (100%); α/β ** = 0.02	generator $^{229}Th \rightarrow {}^{225}Ac \rightarrow {}^{213}Bi$
^{211}At	7.21	α − 5.9 (42)	cyclotron
^{225}Ac	240.2	α − 5.7 (100%)	generator $^{229}Th \rightarrow {}^{225}Ac$
^{223}Ra	273.6	α − 5.7 (100%)	cyclotron
^{149}Tb	4.1	α − 4.0 (~80%)	cyclotron
^{226}Th	0.5	α − 6.3 (~50%)	generator $^{230}U \rightarrow {}^{226}Th$
^{227}Th	448.8	α − 6.0 (48%)	generator $^{227}Ac \rightarrow {}^{227}Th$
^{89}Sr	1212	β − 1.5 (100%)	nuclear reactor
^{153}Sm	46.3	β − 0.81 (100%)	cyclotron

* Percentage of quanta with the indicated energy value in the total amount of quanta of this type emitted by a given radionuclide; ** Ratio of the amount of quanta of different emission types.

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Commercial Name (Other Names)	Antigen/Radionuclide	Disease	Clinical Trial Status
Zevalin (^{90}Y–ibritumomab tiuxetan)	CD20/^{90}Y	non-Hodgkin's lymphoma	Approved by FDA
Bexxar (^{131}I–tositumomab)	CD20/^{131}I	non-Hodgkin's lymphoma	Approved by FDA
Oncolym (^{131}I–Lym 1)	HLA-DR10/^{131}I	non-Hodgkin's lymphoma, chronic lymphocytic leukaemia	Phase III
Lymphocide (Epratuzumab)	CD22/^{90}Y	non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, immune diseases	Phase III
Cotara (^{131}I–chTNT–1/B)	DNA/^{131}I	glioblastoma, anaplastic astrocytoma	Phase III
Labetuzumab (CEA–Cide)	CEA/^{90}Y or ^{131}I	breast, lung, pancreatic, stomach, colorectal carcinoma	Phase III
Theragin (Pemtumomab)	PEM/^{90}Y	ovarian, gastric carcinoma	Phase III
Licartin (^{131}I–metuximab)	(Hab18G/CD147)/^{131}I	hepatocellular carcinoma	Phase II
Radretumab (^{131}I–L19)	Fibronectin/^{131}I	hepatological malignancy, refractory Hodgkin's lymphoma, non-small cell lung cancer, melanoma, head and neck carcinoma	Phase II
PAM4 (^{90}Y–clivatuzumab tetraxetan)	MUC1/^{90}Y	Pancreatic adenocarcinoma	Phase III
Xofigo (^{223}Ra dichloride)	–/^{223}Ra	metastatic castration-resistant prostate cancer	Approved by FDA
Lutathera (^{177}Lu–DOTA–Tyr^{3}–Octreotate)	SST/^{177}Lu	metastatic GastroEnteroPancreatic NeuroEndocrine Tumors	Phase III
^{131}I–MIBG	norepinephrine (NE)/^{131}I	neuroblastoma, Pheochromocytoma, Paraganglioma	Phase III