2° S. IL DOLORE DA METASTASI OSSEE UN DOLORE DIFFIICILE DALLA FISIOPATOLOGIA ALLA PRATICA CLINICA: QUALI ARMI E QUALI NOVITA'?
Moderatori: F. Cognetti, V. Donato, A. Antonuzzo

La medicina nucleare nella diagnosi e trattamento delle metastasi ossee

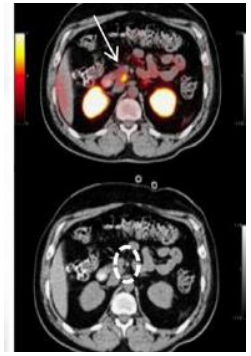
Stefano Severi

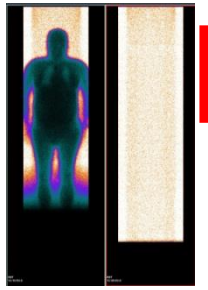
Direttore SS Medicina Nucleare Terapia - IRST Meldola

ISTITUTO ROMAGNOLO PER LO STUDIO DEI TUMORI DINO AMADORI

Targeted Radionuclide Therapies

Diagnosis

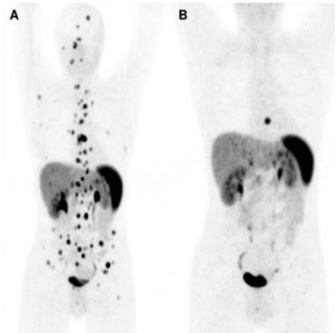




Dosimetry

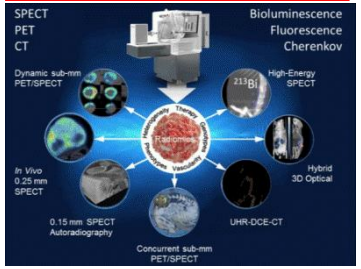
$$t = \frac{1}{\mu_{57Co}} \ln\left(\frac{I_0}{I(t)}\right)$$

Prognosis



Therapy

Radiomics



jove Journal of Visualized Experiments www.jove.com

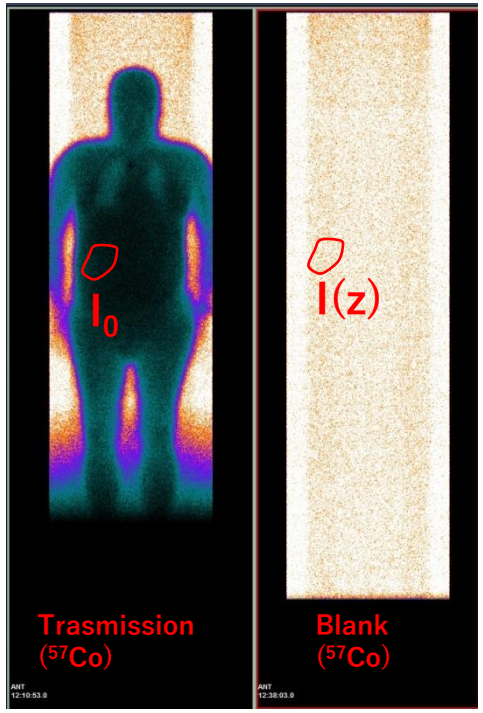
Video Article

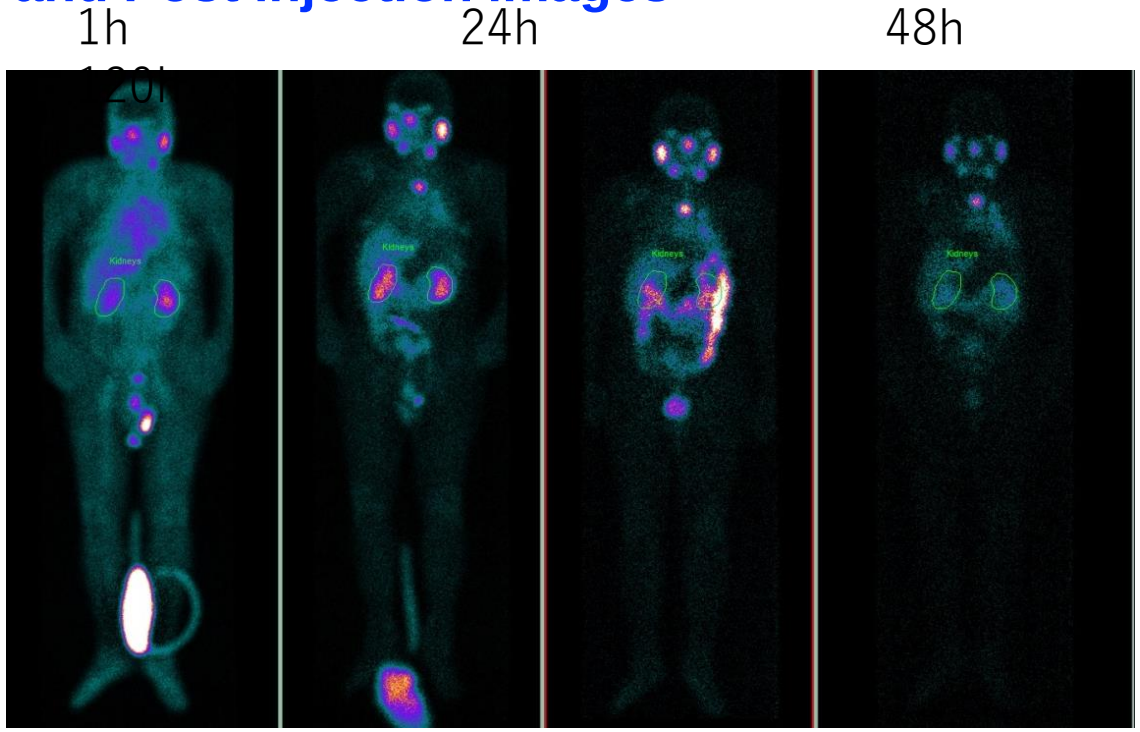
A Whole Body Dosimetry Protocol for Peptide-Receptor Radionuclide Therapy (PRRT): 2D Planar Image and Hybrid 2D+3D SPECT/CT Image Methods

Maria Luisa Belli[1], Emilio Mezzenga[1], Valentina Di Iorio[2], Monica Celli[3], Paola Caroli[3], Elisabeth Canali[3], Federica Matteucci[3], Elisa Tardelli[3], Ilaria Grassi[3], Maddalena Sansovini[3], Silvia Nicolini[3], Stefano Severi[3], Marta Cremonesi[4], Mahila Ferrari[5], Giovanni Paganelli[3], Anna Sarnelli[1]

URL: https://www.jove.com/video/60477
DOI: doi:10.3791/60477

Pre and Post injection images





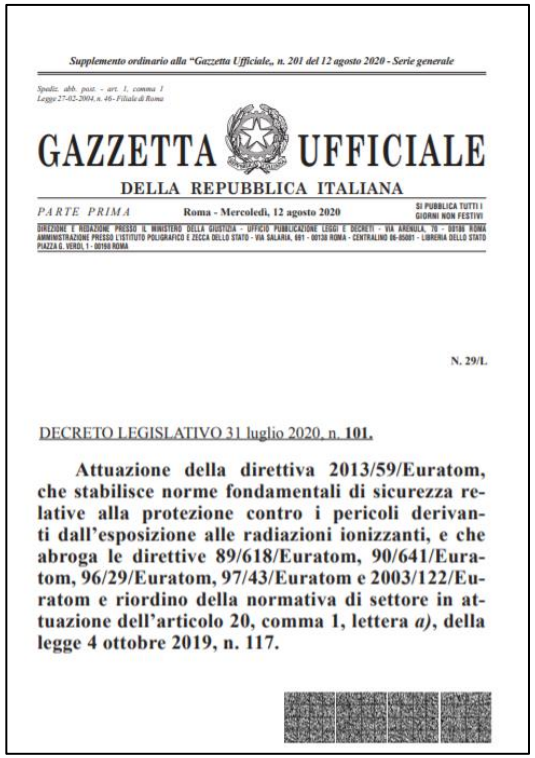
DECRETO LEGISLATIVO 31 luglio 2020, n.101

- Viene recepita la Direttiva Europea 59/2013

- 5 precedenti Direttive Europee sono abrogate tra cui la 96/29 (protezione della popolazione e dei lavoratori) e la 97/43 (esposizioni mediche)

- 4 Decreti Legislativi sono abrogati, tra cui il **DL 230/95** e il **DL 187/00**

Finalmente si raggruppano in un unico corpo le norme di radioprotezione relative ad ambiente, lavoratori ed esposizioni mediche



Supplemento ordinario alla "Gazzetta Ufficiale", n. 201 del 12 agosto 2020 - Serie generale

Spediz. abb. post. - art. 1, comma 1 Legge 27-02-2004, n. 46 - Filiale di Roma

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

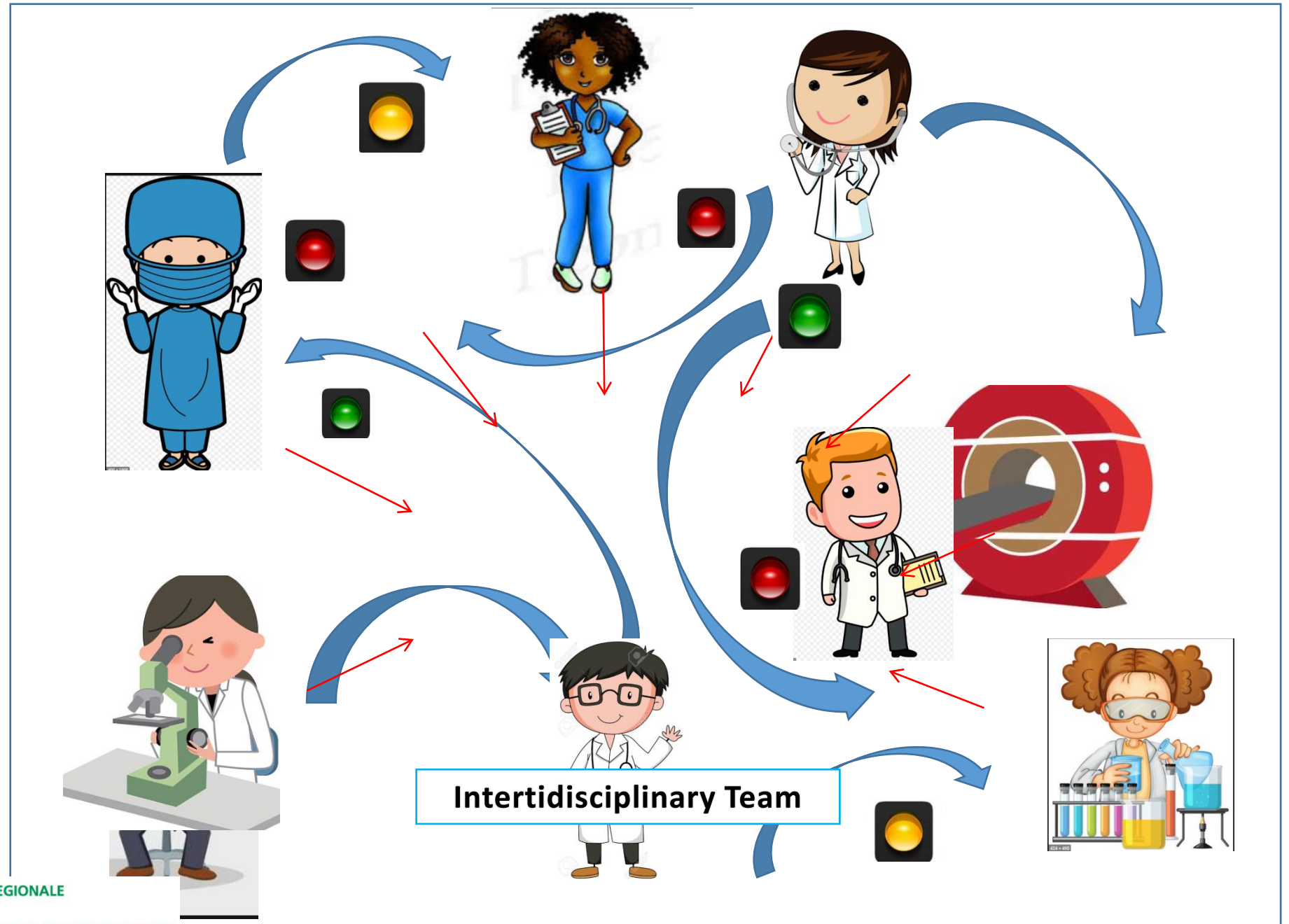
PARTE PRIMA Roma - Mercoledì, 12 agosto 2020 SI PUBBLICA TUTTI I GIORNI NON FESTIVI

DIREZIONE E REDAZIONE PRESSO IL MINISTERO DELLA GIUSTIZIA - UFFICIO PUBBLICAZIONE LEGGI E DECRETI - VIA ARENULA, 70 - 00186 ROMA AMMINISTRAZIONE PRESSO L'ISTITUTO POLIGRAFICO E ZECCA DELLO STATO - Via SALARIA, 691 - 00138 ROMA - CENTRALINO 06-85081 - LIBRERIA DELLO STATO PIAZZA G. VERDI, 1 - 00198 ROMA

N. 29/L.

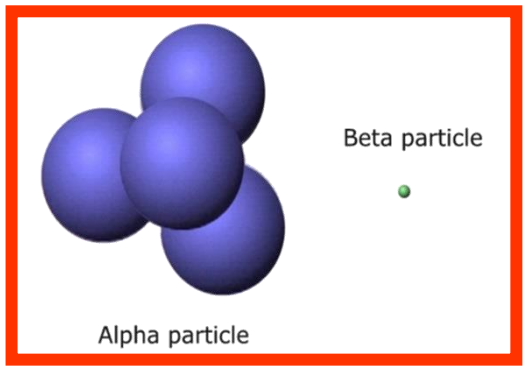
DECRETO LEGISLATIVO 31 luglio 2020, n. **101.**

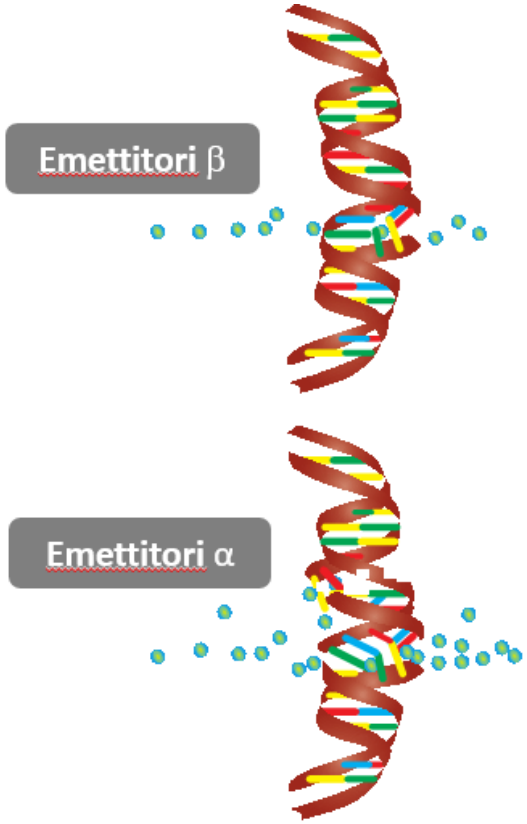
Attuazione della direttiva 2013/59/Euratom, che stabilisce norme fondamentali di sicurezza relative alla protezione contro i pericoli derivanti dall'esposizione alle radiazioni ionizzanti, e che abroga le direttive 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom e 2003/122/Euratom e riordino della normativa di settore in attuazione dell'articolo 20, comma 1, lettera *a)*, della legge 4 ottobre 2019, n. 117.


Intertidisciplinary Team

U-235 -> Th-231 -> Pa-231 -> Ac-227 -> Th-227 -> Ra-223 -> Rn-219 -> Po-215 -> Pb-211 -> Bi-211 -> Tl-207 -> Pb-207 (stable)

223Ra Adroterapia con α emettitori nella terapia delle metastasi scheletriche da adk prostatico





	Beta	Alfa
Energia iniziale (MeV)	0.05-2.3	5-9
Range nel tessuto (μm)	2000	40–100
Massa delle particelle	1	7000
Colpi sul DNA per uccidere la cellula	100/1000	1–4

The NEW ENGLAND JOURNAL of MEDICINE

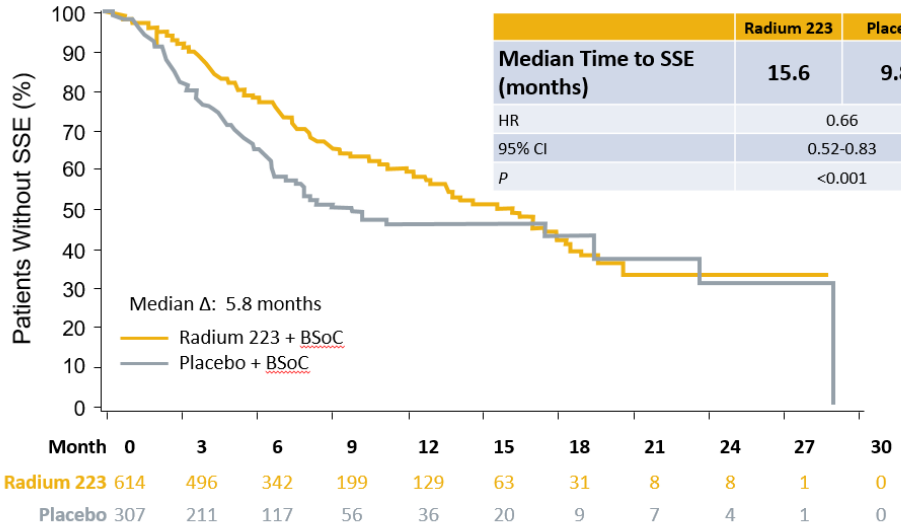
ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Protocol Title:

A double-blind, randomised, multiple dose, Phase III, multicenter study of **Alpharadin** in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases

SSE, Symptomatic Skeletal Events
Parker C, et al. *N Engl J Med.* 2013;369:213-223

ALSYMPCA phase 3 trial: time to first SSE

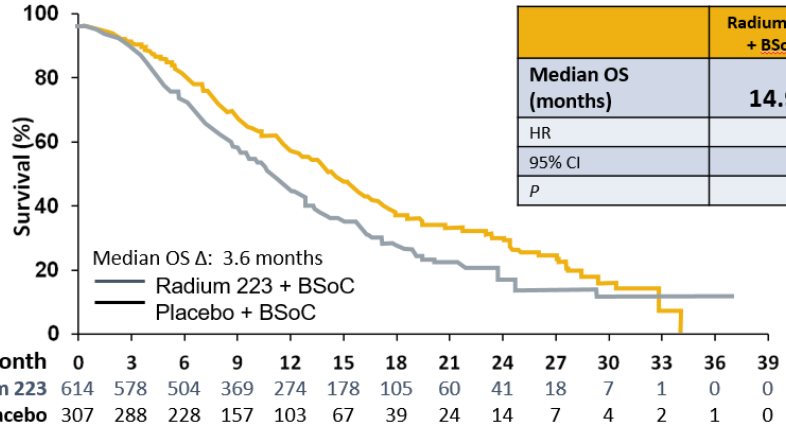


	Radium 223	Placebo
Median Time to SSE (months)	**15.6**	**9.8**
HR	0.66	
95% CI	0.52-0.83	
P	<0.001	

Month	0	3	6	9	12	15	18	21	24	27	30
Radium 223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

BSoC, Best standard of care; SSE, symptomatic skeletal event.

ALSYMPCA phase 3 trial: overall survival



	Radium 223 + BSoC	Placebo + BSoC
Median OS (months)	**14.9**	**11.3**
HR	0.70	
95% CI	0.58-0.83	
P	<0.001	

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Radium 223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

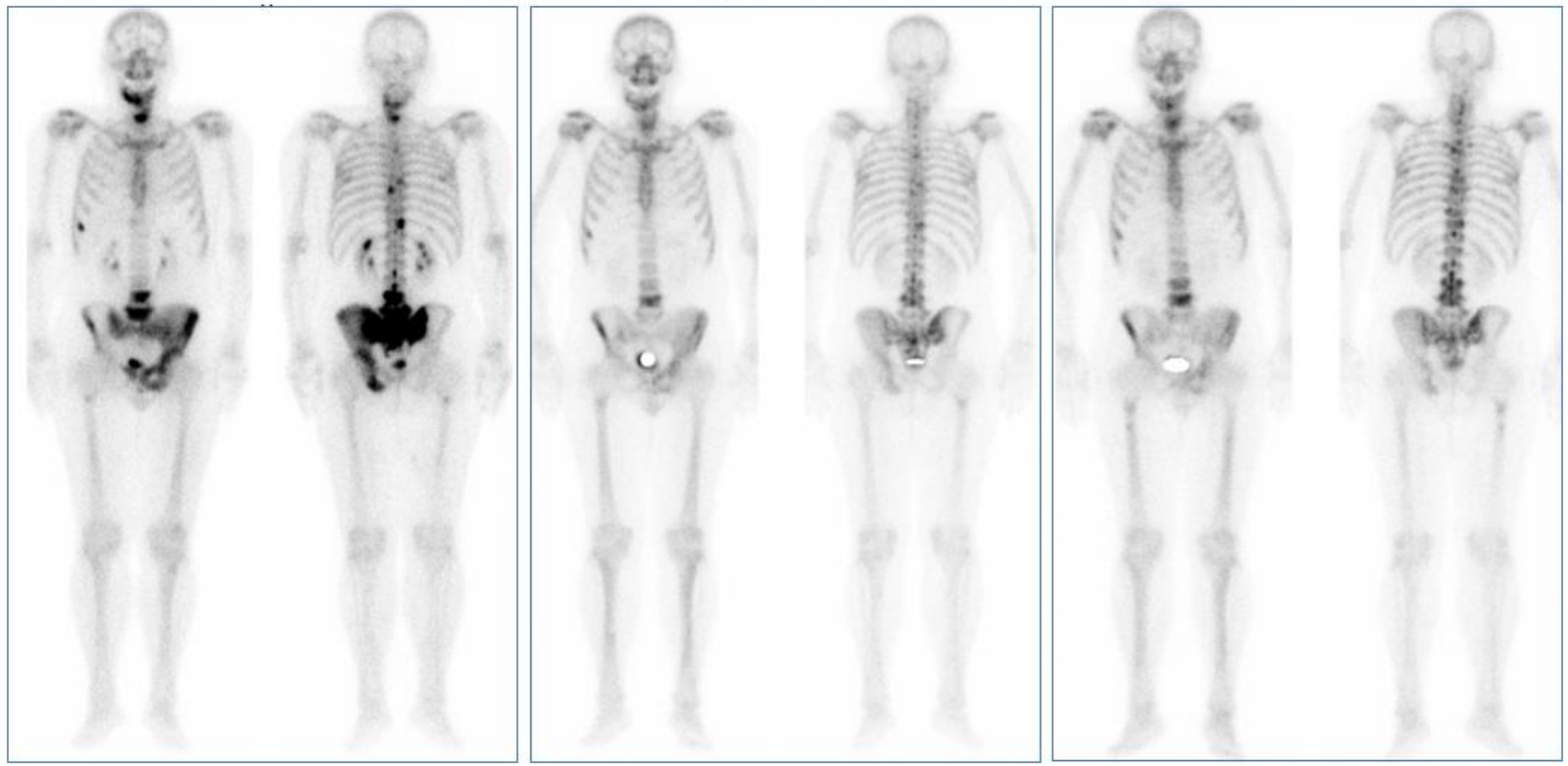
The updated analysis confirmed the interim analysis 30% reduction in risk of death for patients in the radium 223 group compared with placebo.

PERSONAL EXPERIENCE

Basale 05/05/2016

Fine Terapia 30/11/2016

Progressione 22/03/2017



Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

Matthew Smith, Chris Parker, Fred Saad, Kurt Miller, Bertrand Tombal, Quan Sing Ng, Martin Boegemann, Vsevolod Matveev, Josep Maria Piulats, Luis Eduardo Zucca, Oleg Karyakin, Go Kimura, Nobuaki Matsubara, William Carlos Nahas, Franco Nolè, Eli Rosenbaum, Axel Heidenreich, Yoshiyuki Kakehi, Amily Zhang, Heiko Krissel, Michael Teufel, Junwu Shen, Volker Wagner, Celestia Higano

Nel 2019 sono stati pubblicati i risultati dello studio ERA223: studio prospettico prospettico randomizzato disegnato per confrontare l'efficacia di Radium223, un radionuclide alfa emettente, in associazione ad abiraterone + prednisone versus placebo associato ad abiraterone + prednisone nel paziente con malattia resistente alla castrazione metastastatica all'osso [9]. Tale studio, che ha arruolato complessivamente 806 pazienti, è stato interrotto precocemente per il rilievo di un accesso di fratture e decessi nel braccio sperimentale (49%) rispetto al braccio di controllo (47%). Al momento della interruzione dello studio tutti i pazienti avevano comunque completato i cicli di trattamento (Radiom223 o placebo) previsti dal protocollo.

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
MODERATA	L'uso del radio 223 può essere preso in considerazione in II/III linea ed in monoterapia o associato a LHRH in pazienti con metastasi ossee multiple sintomatiche e senza metastasi viscerali da carcinoma prostatico in fase di resistenza alla castrazione anche allo scopo di ridurre gli SRE, di ritardarne la comparsa, di controllare il dolore e di rallentare la progressione scheletrica di malattia. E' consigliabile valutare lo stato dell'osso e associare bifosfonati o denosumab	**Positiva forte**

RAPSON protocol

Randomized, multicentre phase II trial of the sequencing of Radium-223 and Docetaxel plus prednisone in symptomatic bone-only metastatic castration-resistant prostate cancer (mCRPC).

EudraCT number: 2016-004452-29 **CODICE PROTOCOLLO: IRST185.04**

Studio randomizzato, multicentrico, di fase 2 che include pazienti affetti da carcinoma della prostata resistente alla castrazione con metastasi ossee sintomatiche, suddivisi in due bracci di trattamento:

- Braccio A: radium-223 inizialmente seguito da docetaxel più prednisone alla progressione (il secondo step è opzionale in base all'evoluzione clinica della malattia)
- Braccio B: docetaxel più prednisone inizialmente seguito da radium-223 alla progressione (il secondo step è opzionale in base all'evoluzione clinica della malattia)

IRST

ISTITUTO ROMAGNOLO PER LO STUDIO DEI TUMORI DINO AMADORI

ISTITUTO ROMAGNOLO PER LO STUDIO DEI TUMORI DINO AMADORI

International Journal of
Molecular Sciences

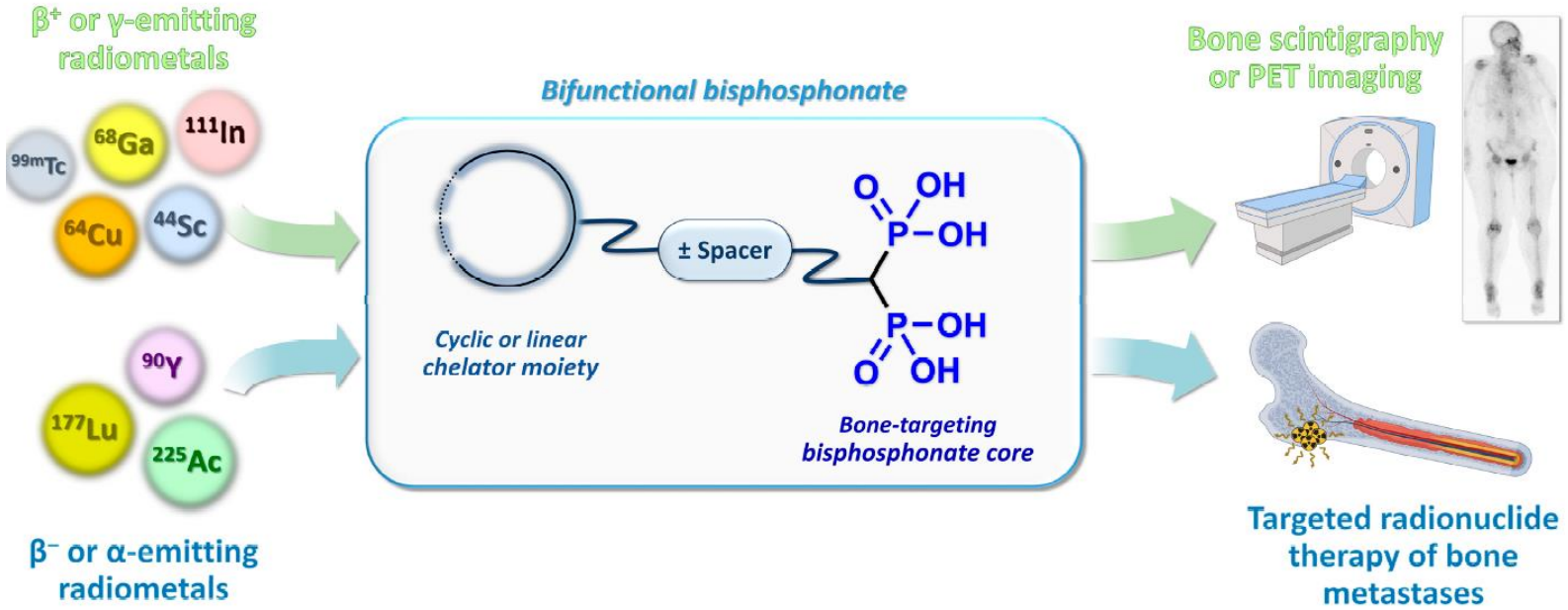
MDPI

Int. J. Mol. Sci. **2024**, *25*, 462. https://doi.org/10.3390/ijms25010462

Review

Bisphosphonates as Radiopharmaceuticals: Spotlight on the Development and Clinical Use of DOTAZOL in Diagnostics and Palliative Radionuclide Therapy

Céleste Souche [1], Juliette Fouillet [1], Léa Rubira [1], Charlotte Donzé [1], Emmanuel Deshayes [1,2] and Cyril Fersing [1,3,*]



DOTA-conjugated zoledronate (DOTAZOL) emerged as an ideal derivative for both **PET imaging** (when **radiolabeled with 68Ga**) and **therapy of bone metastases** from various types of cancer (when **radiolabeled with 177Lu**). In this context, this report provides an overview of the main medicinal chemistry aspects

Endocrine CONNECTIONS

M Scopel *et al.* | 11:7 | e210568

RESEARCH

Endocrine Connections (2022) 11, doi.org/10.1530/EC-21-0568

Bone metastases from neuroendocrine tumors: clinical and biological considerations

Matteo Scopel[1], Eugenio De Carlo[1], Francesca Bergamo[2], Sabina Murgioni[2], Riccardo Carandina[3], Anna Rita Cervino[4], Marta Burei[4], Federica Vianello[4], Vittorina Zagonel[2], Matteo Fassan[5] and Roberto Vettor[1]

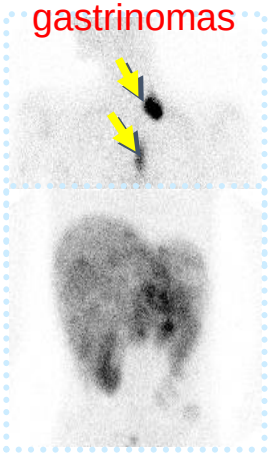
351 patients affected by neuroendocrine tumors (NETs), followed at the University Hospital of Padua and at the Veneto Oncological Institute. Of these, 72 (**20.5%**)

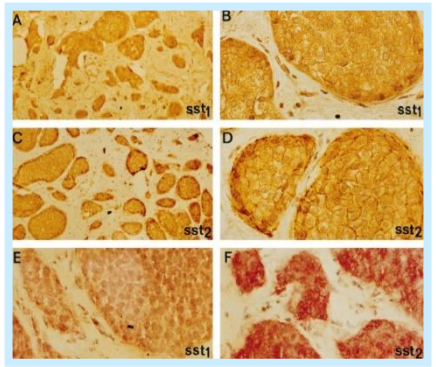
Synchronous metastases generally presents primary tumors with a **higher degree of malignancy**, Ki-67 level. Serious complications are not frequent and not related with the site of the tumor origin with a **cumulative survival rate of 33% at 10 years emerges**.

The **average survival is 80 months** while the median is 84 months. In our observation period, **synchronous patients** had a worse prognosis than metachronous ones with **52-months** survival rates

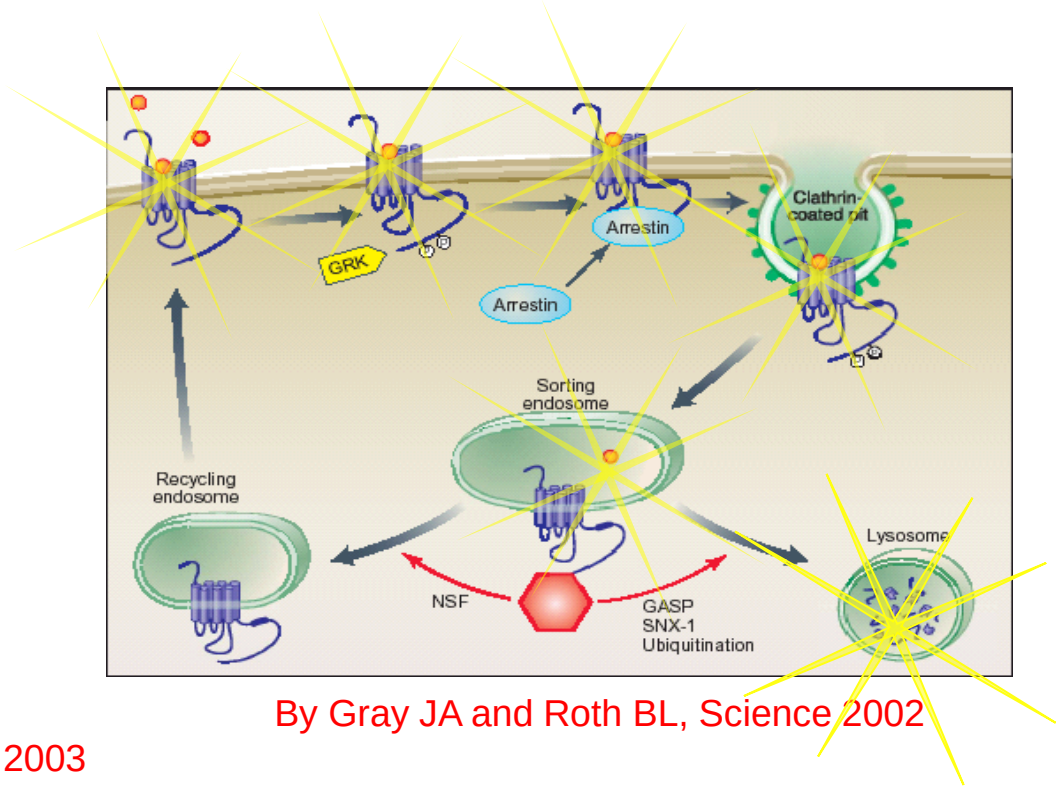
Rationale basis of the radioligand binding in NETs

Metastatic gastrinomas





Lamberts SWJ, Hofland LJ. Endocr Rev 2003



By Gray JA and Roth BL, Science 2002

PET Clinics
Volume 9, Issue 1, January 2014, Pages 83-90

Patient Selection for Personalized Peptide Receptor Radionuclide Therapy Using Ga-68 Somatostatin Receptor PET/CT

Harshad R. Kulkarni MD, Richard P. Baum MD, PhD

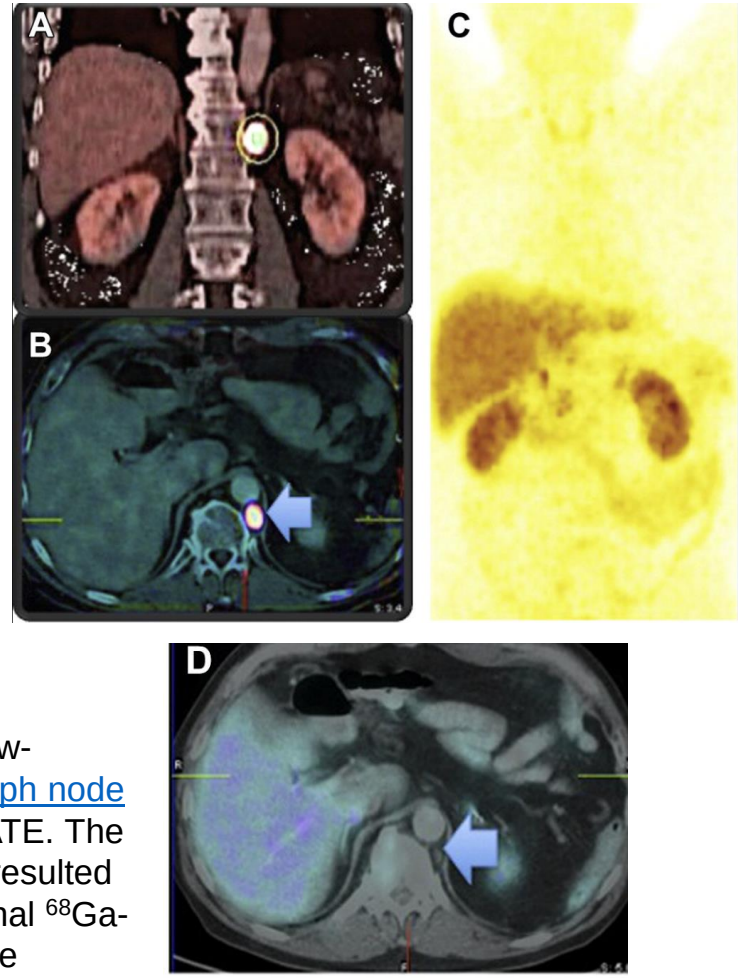
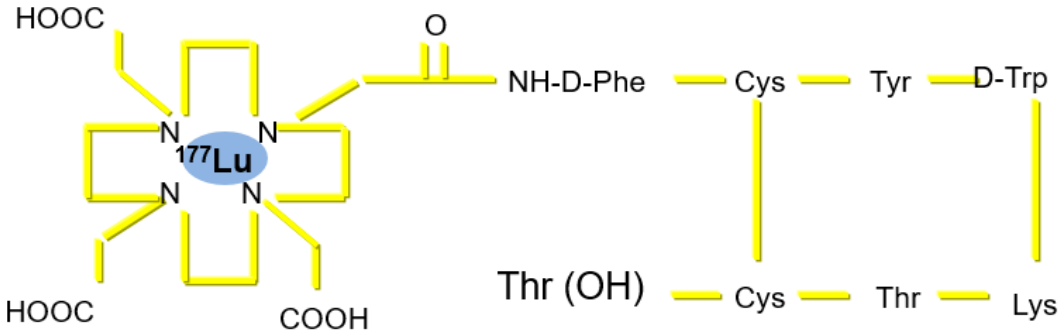


Fig. 1. A 66-year-old patient with well-differentiated, nonfunctioning NET of the pancreas, status post left pancreatectomy, splenectomy, and also metastasectomy in segment 2 of the liver was referred for follow-up ^{68}Ga-SSTR PET/CT after surgery, which revealed a single, very intensely SSTR-positive retrocrural lymph node metastasis with an SUV of 152. Based on this, he underwent 2 cycles of PRRT with 14 GBq ^{177}Lu-DOTATATE. The very high receptor expression and uptake of ^{177}Lu and the resulting high dose delivered to the metastasis resulted in a complete remission according to molecular response criteria, after the 2 PRRT cycles. (*A*) Fused coronal ^{68}Ga-DOTATATE PET/CT before therapy and (*B*) fused transverse image before therapy showing the lymph node metastasis with a *circle* and *arrow*, respectively. (*C*) MIP image of ^{68}Ga-DOTATATE PET/CT after 2 therapy cycles and (*D*) corresponding fused transverse posttherapy image confirmed molecular complete remission, although a small lymph node (*arrow*) is still noted on the CT, which remained stable in size over the next years of follow-up.

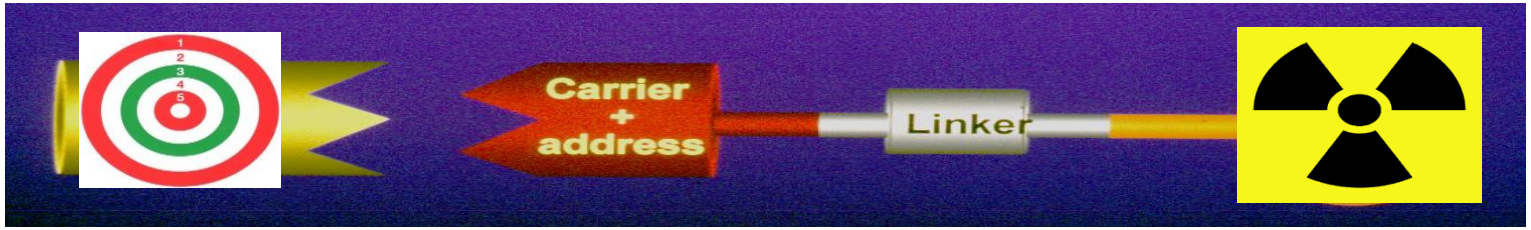
RADIONUCLIDES FOR THERAPY (ELECTRONS)

^{177}Lu	$T_{1/2}$ 6.7 d
	Eγ 0.11 (3%) ; 0.21 (7%) MeV
	E_{max} β$^-$ 0.50 MeV
	R_{max} ~ 1.8 mm

[^{177}Lu-DOTA^0-Tyr^3]-octreotate (^{177}Lu-DOTATATE)



Affinity (IC_{50}, nM)				
sst$_1$	*sst*$_2$	*sst*$_3$	*sst*$_4$	*sst*$_5$
>10,000	1.6 ± 0.4	>1,000	523 ± 239	187 ± 50



The NEW ENGLAND JOURNAL of MEDICINE

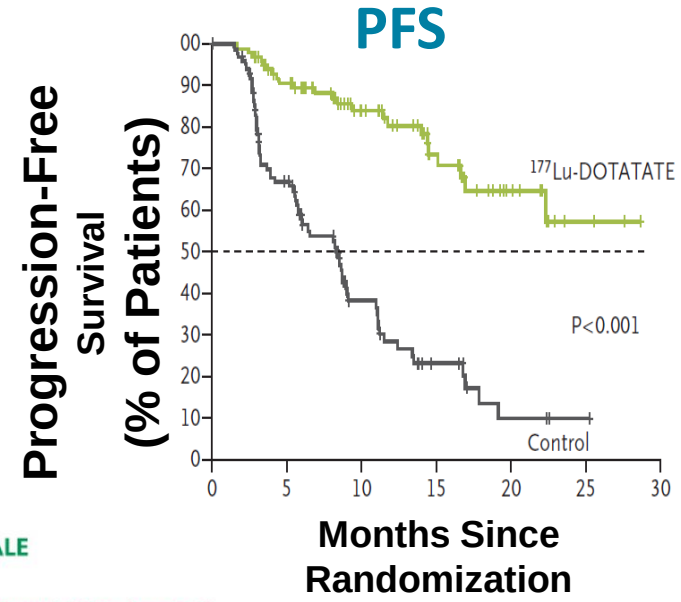
Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-135.

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum,

PFS



The NETTER Study: Trial Design

229 Patients With Midgut NETs

^{177}Lu-DOTATATE group, 116 patients

Control group, 113 patients

^{177}Lu-DOTATATE

7.4 GBq /8 weeks

+

Octreotide LAR

30 mg/4 weeks

Octreotide LAR

60 /mg4 weeks

Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-135.

pharmaceutics

MDPI

Pharmaceutics **2022**, *14*, 189. https://doi.org/10.3390/pharmaceutics14010189

Review

^{212}Pb: Production Approaches and Targeted Therapy Applications

Konstantin V. Kokov [1], Bayirta V. Egorova [2,*], Marina N. German [1], Ilya D. Klabukov [3], Michael E. Krasheninnikov [4], Antonius A. Larkin-Kondrov [1], Kseniya A. Makoveeva [1], Michael V. Ovchinnikov [5], Maria V. Sidorova [5] and Dmitry Y. Chuvilin [1]

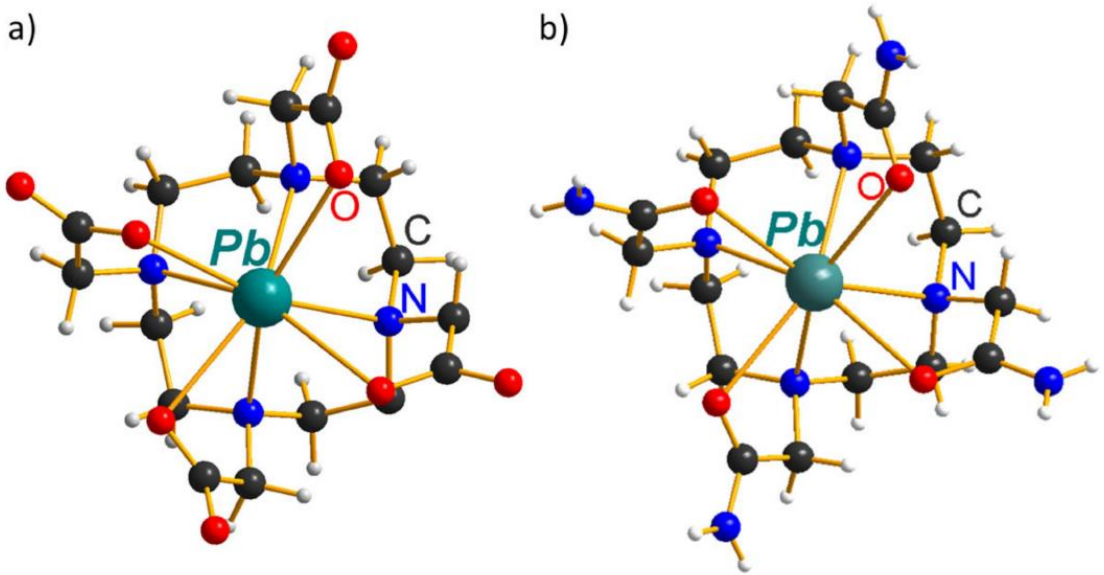


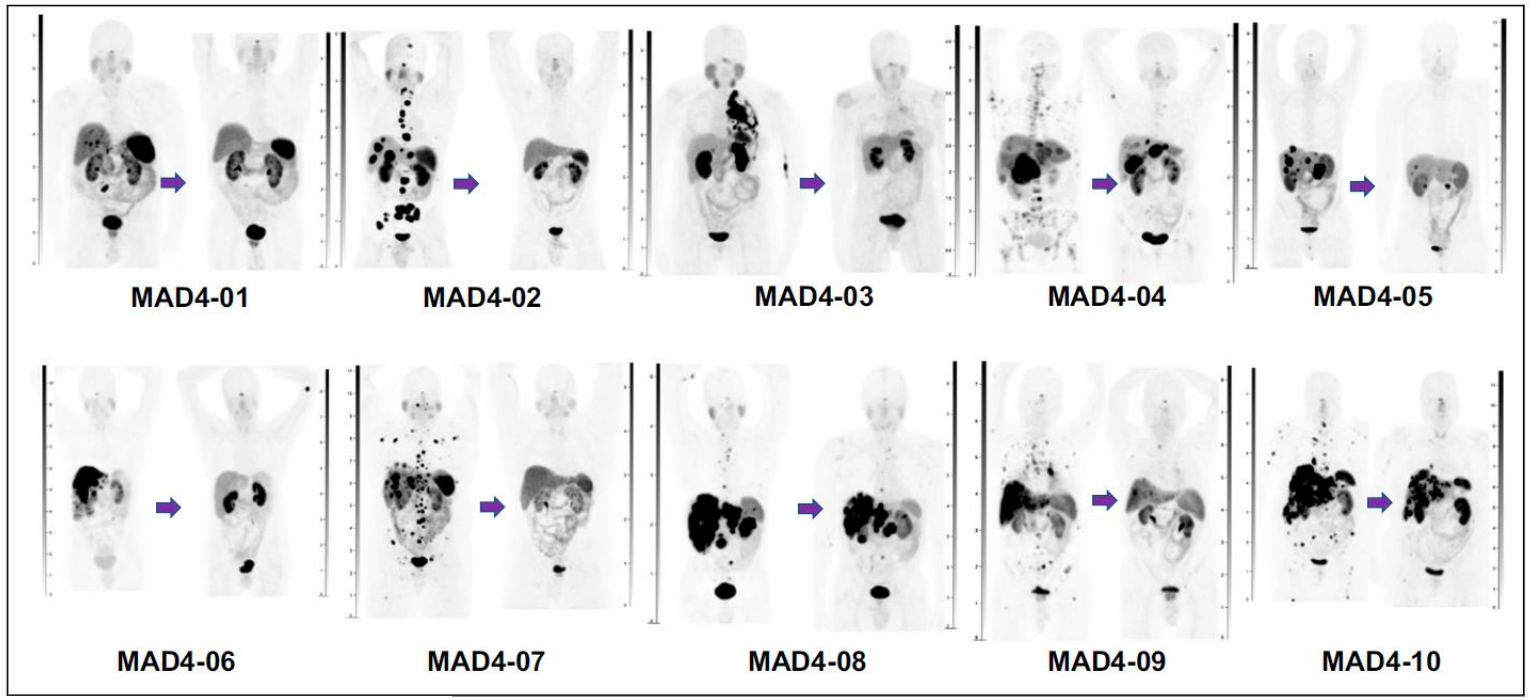
Figure 4. Crystal structure of: (**a**) Pb–DOTA; (**b**) Pb–TCMC complexes.

Lead-212, with a convenient **half-life of 10.64 h**, and **daughter alpha-emitter** short-lived **212Bi (T1/2 = 1 h)**, provides the possibility for the synthesis and purification of complex radiopharmaceuticals with minimum loss of radioactivity during preparation. It can be **milked from a radionuclide generator** in different ways

Targeted α-Emitter Therapy with ^{212}Pb-DOTAMTATE for the Treatment of Metastatic SSTR-Expressing Neuroendocrine Tumors: First-in-Humans Dose-Escalation Clinical Trial

Ebrahim S. Delpassand[1,2], Izabela Tworowska[2], Rouzbeh Esfandiari[1], Julien Torgue[3], Jason Hurt[3], Afshin Shafie[1], and Rodolfo Núñez[1]

J Nucl Med 2022; 63:1326–1333 DOI: 10.2967/jnumed.121.263230

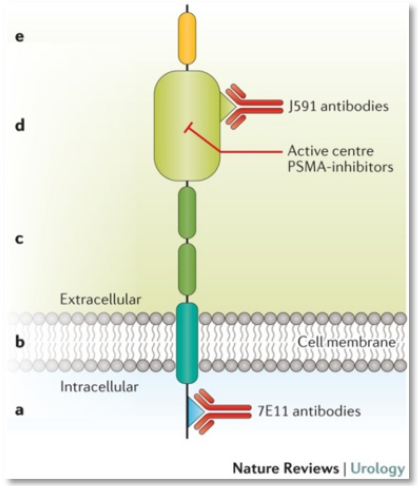


ga-DOTATATE PET/CT scans from first 10 subjects enrolled in cohort 4 (MAD4) before treatment (left side of each panel) with 4 cycles of ^{212}Pb-DOTAMTATE at dose of 2.50 MBq/kg (67.6 μCi/kg) for each cycle.

preliminary results of the **phase 1 first-in-humans dose-escalation trial** evaluating **212Pb-DOTAMTATE** (a bifunctional metal chelator [DOTAM] and the SSTR-targeting peptide [TATE]).
Twenty subjects with histologically confirmed NETs, prior positive somatostatin analog scans, and no prior history of 177Lu/90Y/111In PRRT, with different primary sites of the disease, were enrolled.

ORR by RECIST **was 80%** (1 CR, 7 PR, 2 stable disease) **is 13%** in the **NETTER study**.

PSMA: Prostate Specific Membrane Antigen

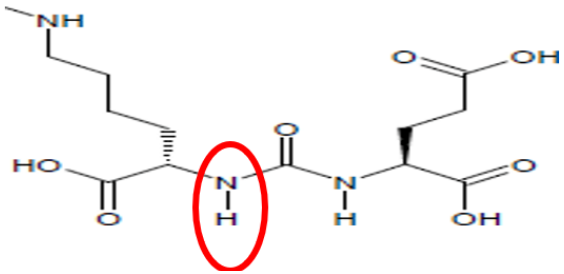


Glicoprotein highly
overespressed in prostatic cancer, as specific target
CARBOSSIPEPTIDASI II (GCPII)

SPECIFIC PSMA INIBITOR

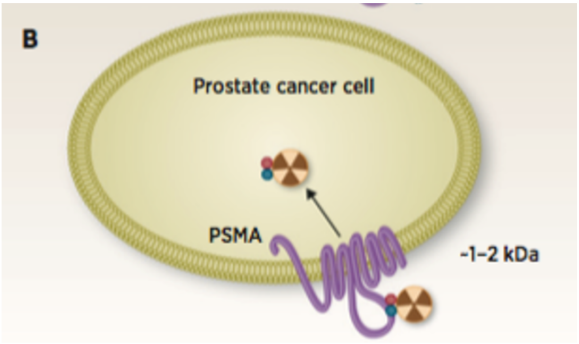
Lysine- urea-glutamate

Lys-NH-CO-NH-Glu:
ureid-based inhibitor of GCPII

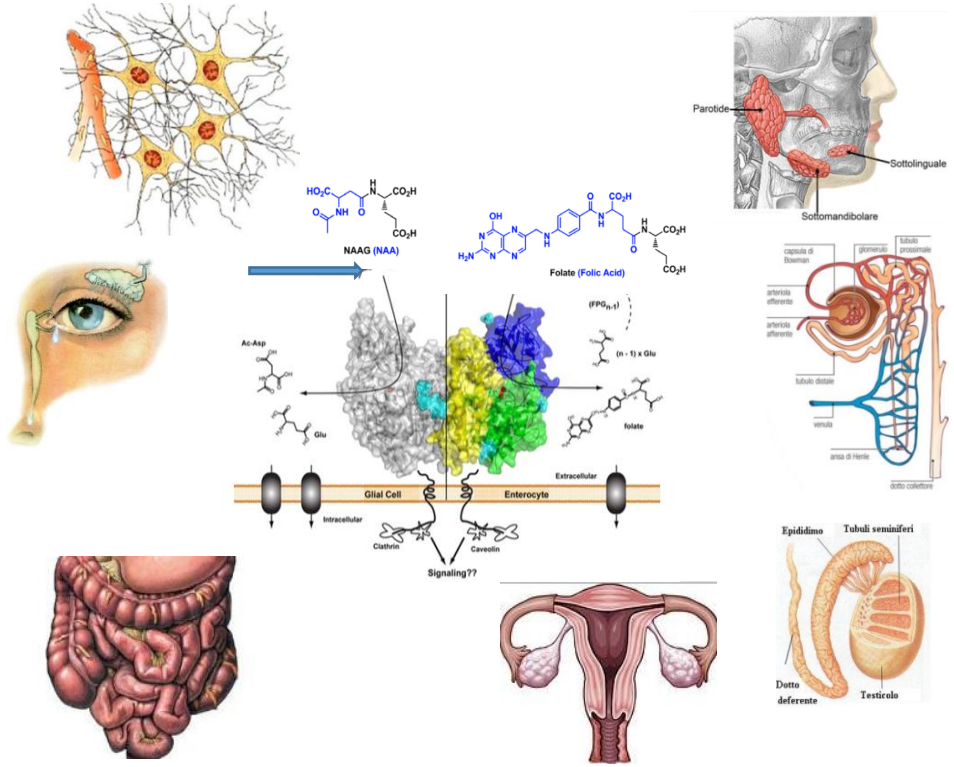


PSMA and PCa

- **PSMA overexpressed on CRPC cells membrane:**
  - Highly specific target
- **PSMA increased expression in:**
  - High Gleason Score
  - CRPC (revCRPC < CRPC < $CRPC_{AA}$)
  - On Testosterone withdrawal
- **PSMA internalisation upon binding with inhibitors:**
  - Suitable for therapy



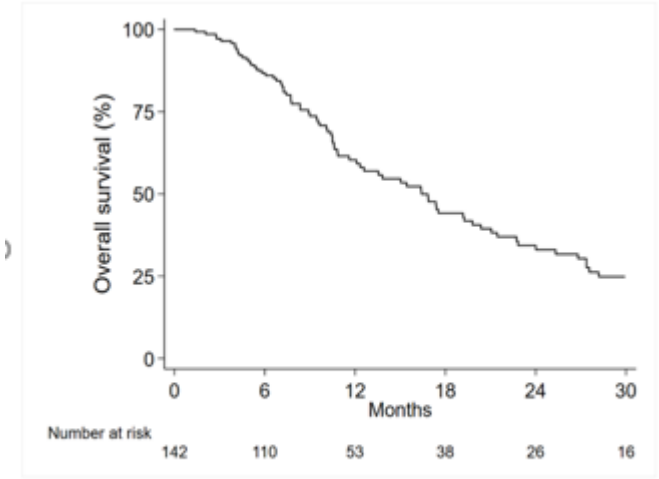
Organ at risk preservation



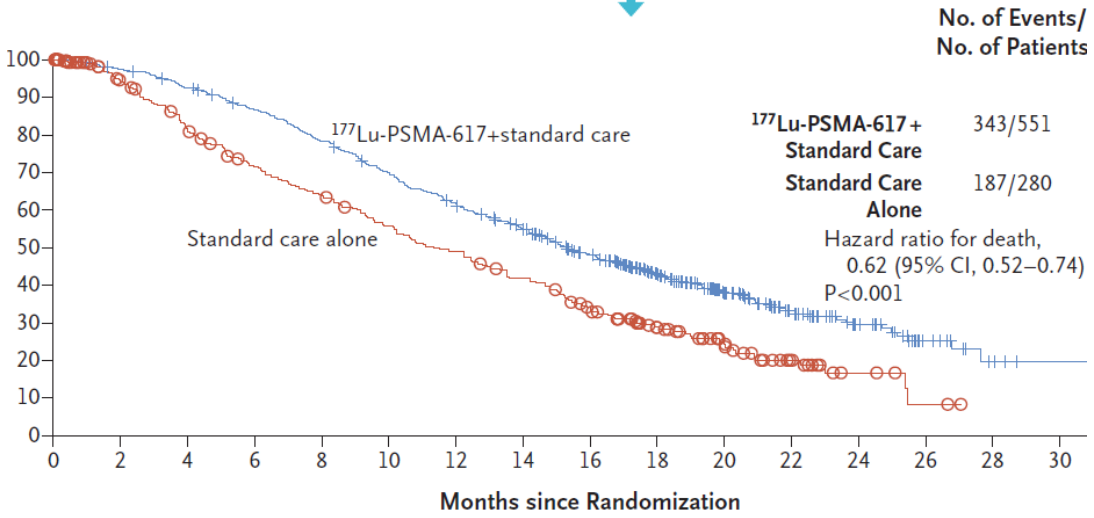
ACTIONS

Kidneys	✓**10% solution of mannitol*** **Intravenously infused** **- 250 ml @ 30 m before RLT** **- 250 ml @ 60 m after RLT**
Salivary glands	✓2 folic polyglutamate candies before and during RLT ✓ Ice pack on the glands
Intestine	✓Laxative solution 6h after RLT

IRST



VISION



	IRST	VISION
Activity/Cycle (GBq)	3·7 – 5·5	7·4
G≥3 toxicity (%)	5	52.7
OS (months)	16,4	15·3

ABSTRACT: RLT with Lu-PSMA in mCRPC patients: could be it feasible before taxane-based chemotherapy? Preliminary results from a phase II clinical trial.

Ilaria Grassi1, Emilio Francesco Giunta2 , Irene Marini1 et all.

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PAZIENTI	Pre Taxani 42pz	Post Taxani 100 pz
Risposta biochimica	23 (54,8%)	35 (35%)
mPFS	8,5 mesi	6 mesi
mOS	35,1mesi	12,6 mesi
Tossicità		anemia G3 (5%)

Methods: in 5 years 145 mCRPC patients were enrolled in the IRST study 185.03. It is a **phase II, open-label, single-centre prospective trial**.
The main endpoint of the trial was best biochemical response (BBR), **main secondary endpoints** were PFS, OS and safety. **142 patients** received up to 6 cycles of Lu-PSMA every 6 weeks, with a **mean dose of 17.5 GBq** (up to 33 GBq of total cumulative dose)

Enzalutamide With Lu PSMA-617 Versus Enzalutamide Alone in Men With Metastatic Castration-resistant Prostate Cancer (ENZA-p)

Detailed Description: open label, randomised, stratified, 2-arm, multicentre phase 2 clinical trial Participants will be randomised to enzalutamide or enzalutamide and Lu-PSMA in a 1:1 ratio.

Primary Outcome Measures:
- Prostate Specific Antigen (PSA) Progression-Free Survival

Secondary Outcome Measures:
- Radiographic Progression-Free Survival
- Prostate Specific Antigen (PSA) response rate (reduction of 50% or more from baseline).

SC/MC-MaM/DG

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Title: A phase II randomized trial of LU-PSMA and Stereotactic Radiotherapy versus Radiotherapy alone for oligometastatic Prostate cancer (LUST)

Protocol Code: IRST 185.09 IRST- identifier Code: L2P2516
Eudract Number: 2022-004151-14

177Lu-PSMA Therapy Versus 177Lu-PSMA in Combination With Ipilimumab and Nivolumab for Men With mCRPC (ANZUP2001)

Detailed Description: open label, **randomised**, **stratified**, **multicentre phase 2** clinical trial, 2:1 ratio stratified by prior exposure to docetaxel.
Design: 177**Lu-PSMA** (7.5GBq) every 6 weeks up to 6 cycles in combination with concurrent ipilimumab and nivolumab followed by nivolumab monotherapy

Primary Outcome Measures:
- PSA progression free survival (PSA-PFS) at 1 year (PCWG3)

Secondary Outcome Measures:
- PSA response rate (PSA-RR) (reduction of ≥ 50% from baseline).
- Frequency and severity of adverse events (CTCAE v5.0)
- Radiological/PSA progression free survival (PCWG3/RECIST1.1)
- Overall survival (OS)

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In Men With mPC, What is the Safety [illegible] etium-177 PSMA Radionuclide Treatment in Addition to Chemotherapy (UpFront PSMA)

Detailed Description: open label, randomised, stratified, 2-Arm, multi- centre, phase 2 clinical trial. Patients will be randomised to the experimental Arm (**177Lu-PSMA followed by docetaxel**) or standard of care Arm (**docetaxel**) in a 1:1 ratio.

Primary Outcome Measures:
- Undetectable (as PSA ≤ 0.2ng/ml) prostate specific antigen (PSA)

Secondary Outcome Measures:
- Safety of 177**Lu-PSMA** followed by docetaxel
- Time to development of mCRPC
- PSA-progression free survival (PSA-PFS)
- Radiographic-PFS (rPFS)
- Overall survival (OS) between treatment Arms

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:860–877
https://doi.org/10.1007/s00259-017-3922-y

REVIEW ARTICLE

Targeting PSMA by radioligands in non-prostate disease—current status and future perspectives

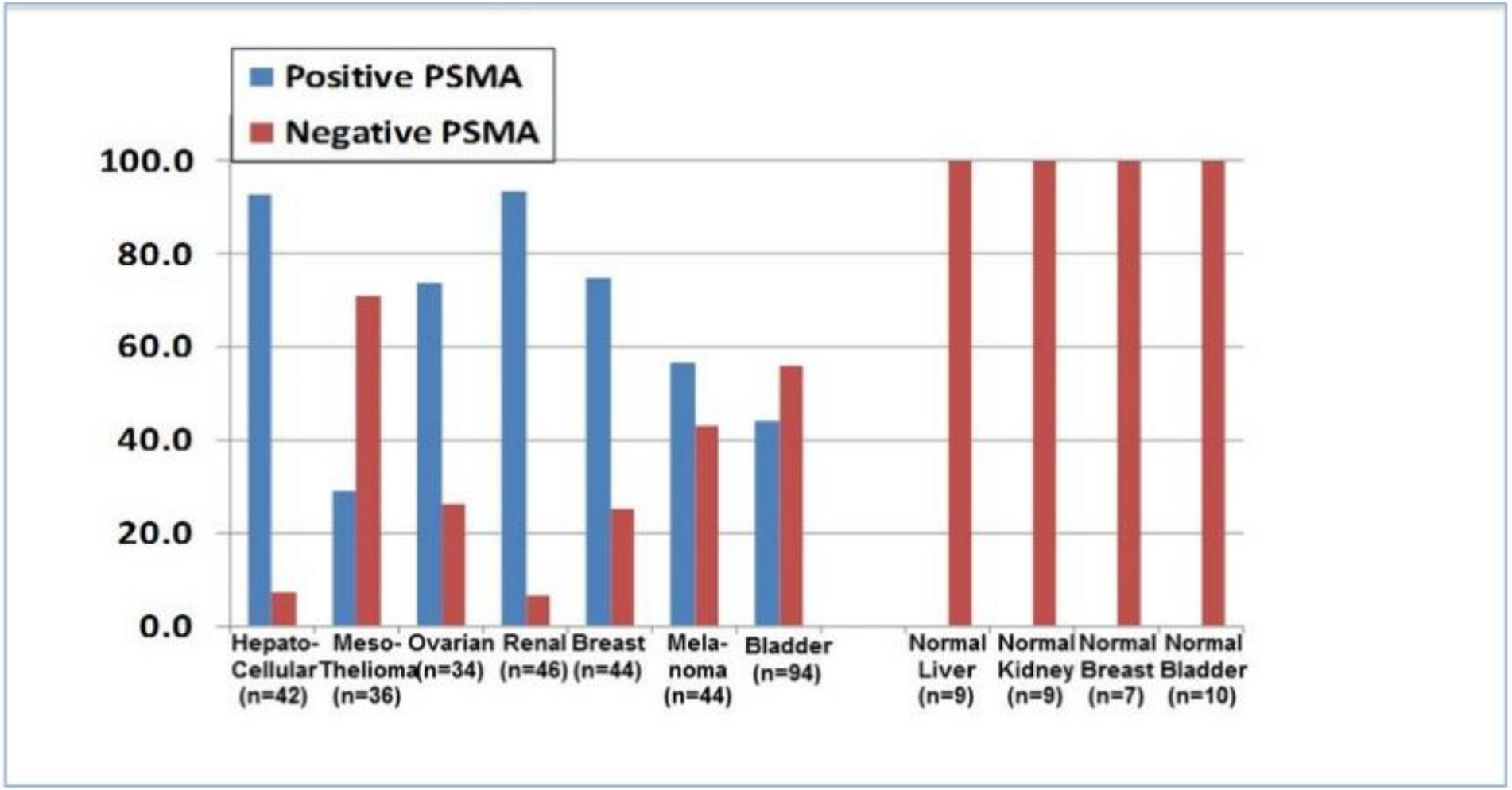
Philipp Backhaus[1,2] · Benjamin Noto[1] · Nemanja Avramovic[1] · Lena Sophie Grubert[1] · Sebastian Huss[3] · Martin Bögemann[4] · Lars Stegger[1] · Matthias Weckesser[1] · Michael Schäfers[1,2] · Kambiz Rahbar[1]

Abstract

Background Prostate-specific membrane antigen (PSMA) is the up-and-coming target for molecular imaging of prostate cancer. Despite its name, non-prostate-related PSMA expression in physiologic tissue as well as in benign and malignant disease has been reported in various publications. Unlike in prostate cancer, PSMA expression is only rarely observed in non-prostate tumor cells. Instead, expression occurs in endothelial cells of tumor-associated neovasculature, although no endothelial expression is observed under physiologic conditions. The resulting potential for tumor staging in non-prostate malignant tumors has been demonstrated in first patient studies. This review summarizes the first clinical studies and deduces future perspectives in staging, molecular characterization, and PSMA-targeted radionuclide therapy based on histopathologic examinations of PSMA expression.

Conclusions The non-exclusivity of PSMA in prostate cancer opens a window to utilize the spectrum of available radioactive PSMA ligands for imaging and molecular characterization and maybe even therapy of non-prostate disease.

PSMA staining in tumor vasculature



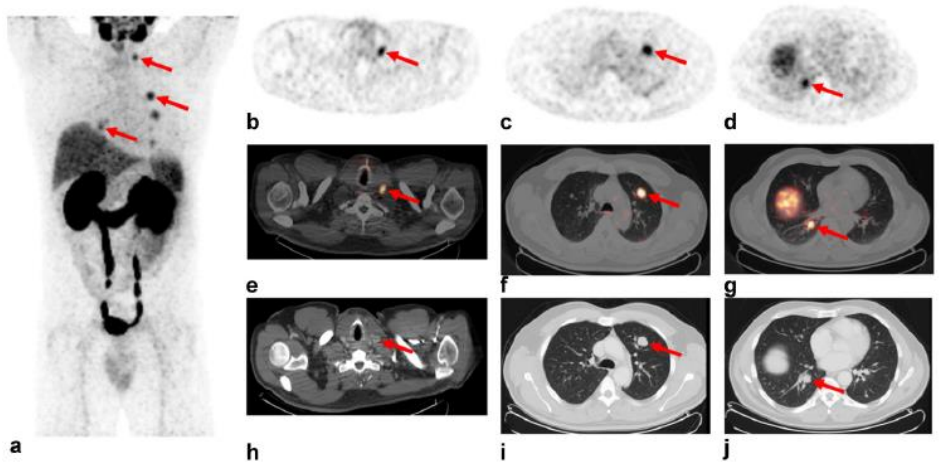
Denmeade, SR et al., Sci. Transl. Med. 4, 140ra86 (2012)

Eur J Nucl Med Mol Imaging (2015) 42:1622–1623
DOI 10.1007/s00259-015-3065-y

IMAGE OF THE MONTH

First evidence of PSMA expression in differentiated thyroid cancer using [^{68}Ga]PSMA-HBED-CC PET/CT

Frederik A. Verburg[1,2] · Thomas Krohn[1] · Alexander Heinzel[1] · Felix M. Mottaghy[1,2] · Florian F. Behrendt[1]



cers such as renal cell carcinoma [3, 4], colon carcinoma, neuroendocrine tumours, melanoma or breast cancer [3]. However, to our knowledge no study has yet investigated

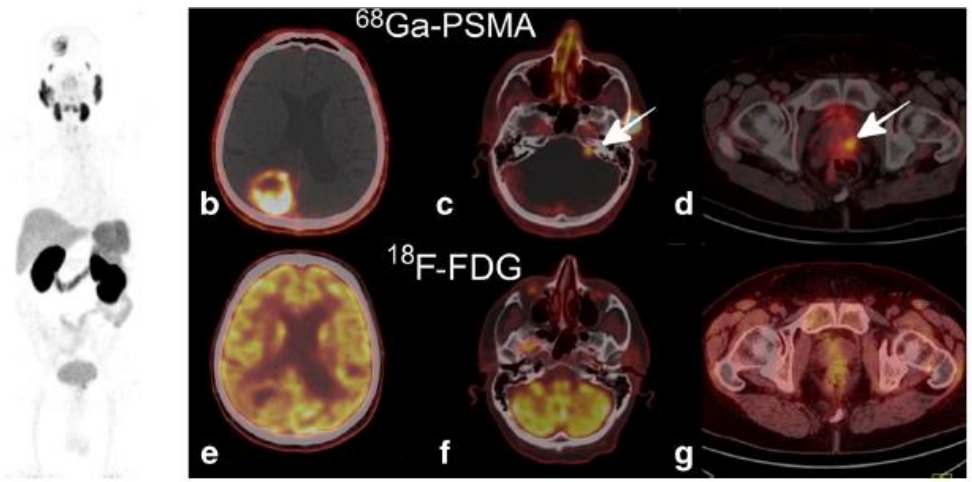
European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:886–887
https://doi.org/10.1007/s00259-018-3934-2

IMAGE OF THE MONTH

Glioblastoma multiforme: another potential application for ^{68}Ga-PSMA PET/CT as a guide for targeted therapy

Jolanta Kunikowska[1] · Królicki Bartosz[2] · Królicki Leszek[1]

Received: 30 October 2017 / Accepted: 2 January 2018 / Published online: 31 January 2018



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OGGETTO: EudraCT number: 2022-003162-20

TITOLO: Terapia radiometabolica (TRM) con 177Lu

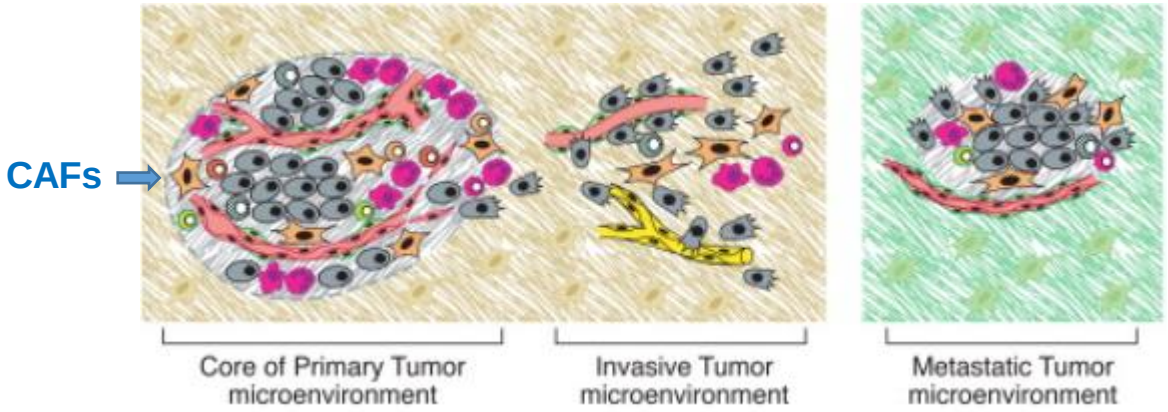
PSMA in tumori avanzati/metastatici positivi alla PET/CT

PSMA: uno studio basket

FAP is a specific and selective marker of cancer-associated fibroblasts (CAFs)

FIBROBLAST Activation Protein (FAP) is highily expressed in CAFs in 90% of all cancer types

- Cancer- associated fibroblasts (CAFs) are **highily prevalent in tumor microenvironment** (TME) of many cancer entities
- CAFs persist in the TME throught **all malignant stages of tumorigenesis**
- CAFs express PAP, which represents a **pan-tumor target**
- FAP is **not expressed on normal fibroblast**, thus FAP expressione is norma tissues in very low



TARGET first described by Wolfang J. Rettig and Lloyd J. Old (MSKCC) 1990

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:709–720
https://doi.org/10.1007/s00259-021-05472-3

ORIGINAL ARTICLE

Increased uptake of ^{68}Ga-DOTA-FAPI-04 in bones and joints: metastases and beyond

Chunxia Qin[1,2] · Yangmeihui Song[1,2] · Xi Liu[3] · Yongkang Gai[1,2] · Qingyao Liu[1,2] · Weiwei Ruan[1,2] · Fang Liu[1,2] · Fan Hu[1,2] · Xiaoli Lan[1,2]

Received: 4 April 2021 / Accepted: 17 June 2021 / Published online: 9 July 2021

The **detectability of malignant and benign bone lesions** using **68Ga-FAPI PET and 18F-FDG P**ET was compared.

Elevated uptake of **68Ga-FAPI was found in 82/129 cases** (63.57%). A total of **295 lesions** were identified, including **94 (31.9%) malignant lesions (all were metastases) and 201 (68.1%) benign lesions**. **68Ga-FAPI PET identified much more lesions than 18F-FDG PET (104 vs. 48)** with higher uptake value.

Bone metastases were mainly distributed in the spine, pelvis, and ribs.

The mean SUVmax of bone metastases was significantly higher than that of benign diseases (7.14 ± 4.33 vs. 3.57 ± 1.60, $p < 0.001$), but overlap existed.

The differences in SUVmax among subgroups of benign diseases was also registered and were statistically significant ($p < 0.001$),

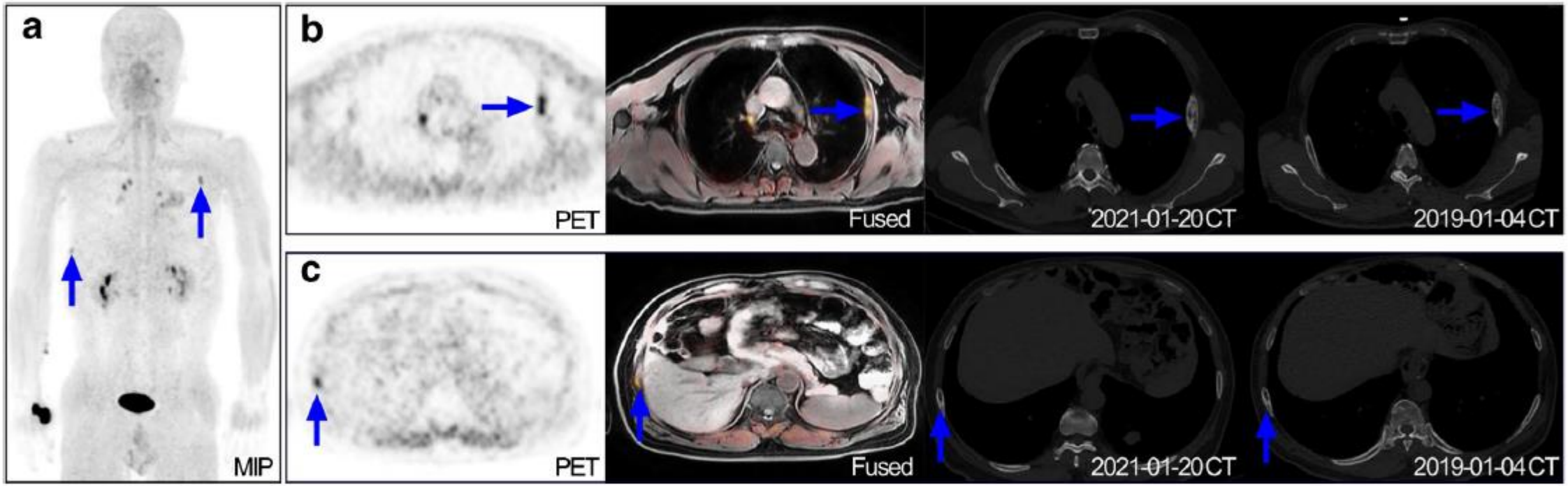
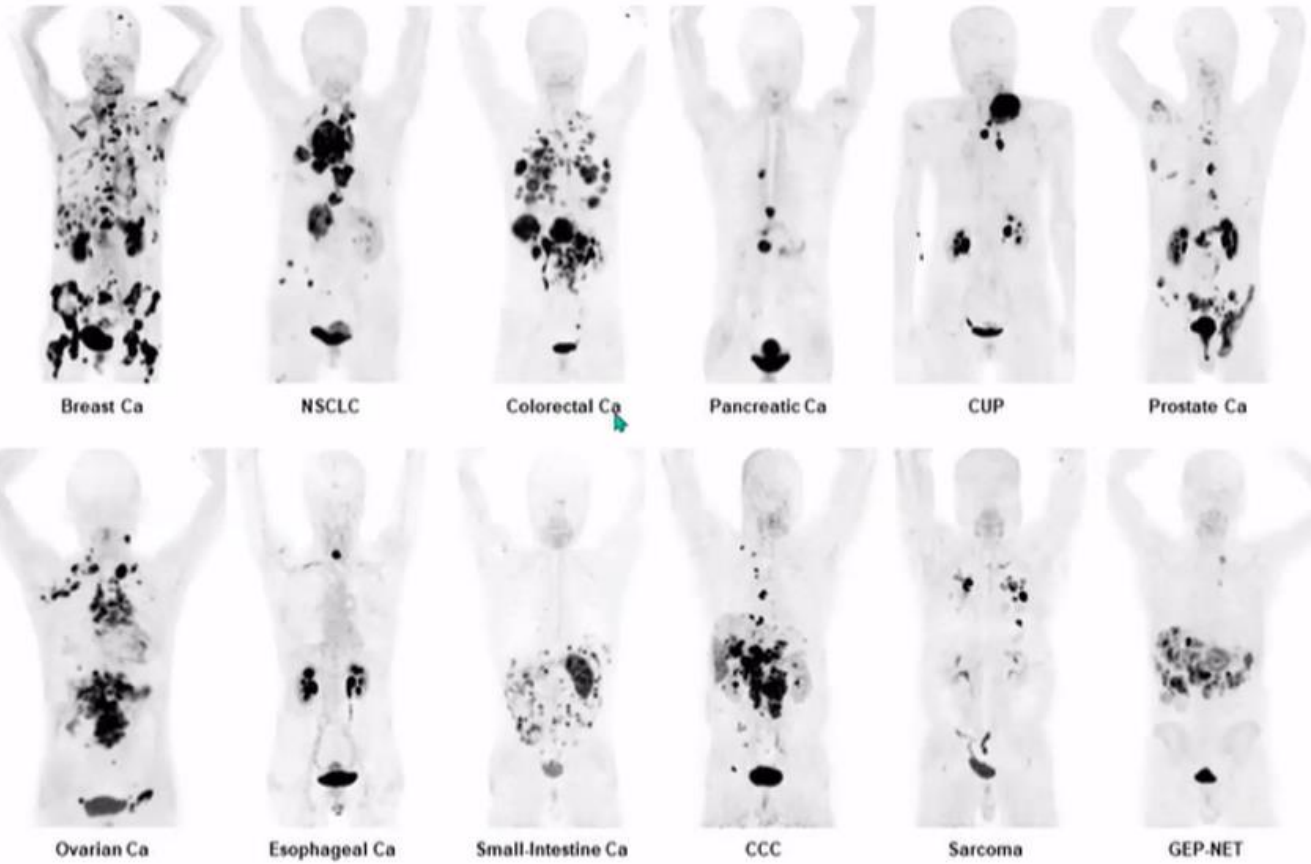


Fig. 4 A 58-year-old male underwent ^{68}Ga-FAPI PET/MR for detecting recurrence and metastases after 5-year comprehensive treatment of gastric cancer. Aggregation of ^{68}Ga-FAPI on the left fourth rib (**a** and **b**, blue arrows) and right ninth rib (**a** and **c**, blue arrows) appeared with heterogeneous signals on MR (**b** and **c**, blue arrows on fused images), corresponding to well-demarcated lesions with irregular ground-glass opacities and part of low-density shadow on the recent CT, same as CT 2 years ago (**b** and **c**, blue arrows on CT images). From the medical history and imaging findings, the two lesions were highly suspected as osteofibrous dysplasia

FAPI-PET in different kinds of cancer



GEP-NET

SNMMI 2019 Image of the Year:

^{68}Ga-FAPI-PET/CT in patients reflecting 12 different tumor entities. Ca = cancer; NSCLC = non-small cell lung cancer; CUP = carcinoma of unknown primary; CCC = cholangiocarcinoma; GEP-NET= Gastroenteropancreatic neuroendocrine tumor.

Image Credit: *Image created with contributions from Clemens Kratochwil, Paul Flechsig, Thomas Lindner, Labidi Abderrahim, Annette Altmann, Walter Mier, Sebastian Adeberg, Hendrik Rathke, Manuel Röhrich, Hauke Winter, Peter Plinkert, Frederik Marme, Matthias Lang, Hans Ulrich Kauczor, Dirk Jaeger, Juergen Debus, Uwe Haberkorn,* ***Frederik L. Giesel****; all contributors are affiliated with University Hospital Heidelberg, Germany.*

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	68 Gallium-Fibroblast Activating Protein Inhibitors-46 Positron Emission Tomography - Computerized Tomography for Molecular Assessment of Fibroblast Activation and Risk Assessment in Solid Tumors	• Solid Tumor, Unspecified, Adult	• Diagnostic Test: 68 Gallium - Fibroblast Activating Protein Inhibitor -46 Positron emission tomography / Computerized tomography	• IRCCS Istituto ROmagnolo per lo Studio dei Tumori "Dino Amadori"-IRST S.r.l. Meldola, Forlì Cesena, **Italy**

Sensibilità diagnostic della PET 68Ga-FAPI nei vari tipi d tumori ed in particolare nei sarcomi

Protocollo propedeutico a successive protocollo terapeutico di fase II con 177Lu-FAPI

Federica Matteucci, **Severi Stefano**, Maddalena Sansovini, Silvia Nicolini, Ilaria Grassi, Irene Marini, Paola Caroli, Anna Sarnelli, Maria Luisa Belli, Valentina Di Iorio, Manuela Monti, Monica Golinucci, Giovanni Paganelli and many others!!!

stefano.severi@irst.emr.it

212 PB theray in NET. The study was designed as a single-ascending-dose (SAD)/multiple-ascending-dose (MAD) trial using a 3 1 3 dose-escalation scheme with an 8-wk dose-limiting toxicity period.
The maximum total dose per subject in the **SAD** cohort was 296 MBq (8 mCi). The maximum total dose per subject in the **MAD** cohort was 888 MBq (24 mCi).
Thirty minutes before each dose, an amino acid solution of lysine and arginine was administered at 250mL/h over 4 h for **kidney protection**.

The primary endpoint was assessment of the **safety and dose-limiting tox**icities of ascending doses of 212Pb-DOTAMTATE used for TAT of subjects with SSTR-expressing NETs. **Secondary endpoints** included **pharmacokinetics, dosimetry,** and determination of preliminary **effectiveness** of 212Pb-DOTAMTATE.

RESULTS
In the MAD4 cohort, the **ORR** by RECIST was **80% (1 CR, 7 PR, 2 stable disease).**
NETTER-1 study, in last updated data registered a 13% ORR in the 177Lu-DOTATATE group and 4% in the control group

SAFETY
No dose-limiting toxicities were noted during dose escalation or expansion, and **no subject required a delay in treatment or a reduction of dose**.

RAZIONALE

Le metastasi ossee rappresentano una sfida significativa nel panorama oncologico a causa dell'impatto sulle morbilità e sulla qualità della vita dei pazienti. L'osso è il terzo sito più comune di metastasi per diversi tipi di cancro, inclusi quelli della mammella, della prostata e del polmone, e può portare a eventi scheletrici correlati come dolore, fratture patologiche, ipercalcemia e necessità di radioterapia o chirurgia.
L'evento si propone di esplorare gli ultimi sviluppi e le strategie terapeutiche più avanzate nel trattamento delle metastasi ossee, una complicazione frequente in pazienti con neoplasie in stadio avanzato.
L'obiettivo è quello di condividere e discutere i progressi recenti nella ricerca, nonché le opzioni cliniche attuali che possono migliorare la qualità della vita dei pazienti e gestire in modo più efficace questa condizione.

PROGRAMMA SCIENTIFICO

08.30 **Saluti**
08.45 **Presentazione del Corso** T. Ibrahim, G. Lanzetta

1° S. INQUADRAMENTO DELLE METASTASI OSSEE: LA CLINICA, L'IMAGING E LA BIOLOGIA MOLECOLARE

Moderatori: L. Mercatali, D. Santini, M. Stefanini, R. Pedersini

09.00 **L'osteoncologia nel 2024** T. Ibrahim
09.15 **Linee Guida Aiom 2023: metastasi ossee e salute dell'osso** D. Santini
09.30 **L'imaging nella diagnosi delle metastasi ossee** A. Laghi
09.45 **Limiti della Biopsia ossea nell'era dell'Oncologia di Precisione** G. Perrone
10.00 **Metastasi ossee e tumore della mammella: l'importanza delle Cicline e impatto sull'osso e sul dolore** F. Pantano
10.15 **Metastasi ossee e tumore della prostata: ruolo degli ARI e dei PARP- Inihibitor loro Impatto sull'osso e sul dolore** M. Bergamini
10.30 **Discussione tutti i partecipanti**

10.45 Coffee Break

2° S. IL DOLORE DA METASTASI OSSEE UN DOLORE DIFFIICILE DALLA FISIOPATOLOGIA ALLA PRATICA CLINICA: QUALI ARMI E QUALI NOVITA'?

Moderatori: F. Cognetti, V. Donato, A. Antonuzzo

11.00 LETTURA **La Fisiopatologia, la Ricerca e la terapia del dolore da metastasi ossee** G. Lanzetta
11.30 **NICSO: L'importanza delle terapie di supporto nel paziente con metastasi ossee** A. Antonuzzo
11.45 **Bone Targeted Therapy** T. Falbo
12.00 **La medicina nucleare nella diagnosi e trattamento delle metastasi ossee** S. Severi
12.15 **Nuovi approcci della Radioterapia nelle metastasi ossee** F. Cellini
12.30 **Scrambler therapy e criotherapy nel dolore neuropatico oncologico** D. Russo
12.45 **Gli approcci endovascolari nelle metastasi ossee** G.Facchini
13.00 **Le procedure RM guidate, realtà e futuro nel trattamento delle metastasi ossee** M. Stefanini
13.15 **Discussione tutti i partecipanti**

13.30 Lunch

3° S. TRATTAMENTI LOCOREGIONALI, LA CHIRURGIA E LA RIABILITAZIONE: QUALI LIMITI E QUALI NOVITA'

Moderatori: R. Biagini, T. Ibrahim, A. Del Conte, S. Zovato

14.30 **L'ipertermia nel controllo del dolore oncologico limiti e applicazioni** A. Costa
14.45 **L'Elettrochemioterapia nel trattamento delle metastasi ossee** L. Campanacci
15.00 **L' approccio chirurgico nelle metastasi delle ossa lunghe** R. Casadei
15.15 **L' Approccio Chirurgico nelle metastasi delle ossa Rachide e Bacino** C. Zoccali
15.30 **Presentazione Nuovi Studi di Laboratorio e Clinici ISO** L. Mercatali, A. Del Conte, S. Zovato
15.50 **Risultati Survey ISO Terapie Locoregionali** L. Campanacci, G. Facchini
16.15 **Discussione tutti i partecipanti**

16.30 **Take home message e conclusioni** G. Lanzetta,T. Ibrahim, D. Santini