

Teranósticos na clínica: Estado da arte e perspectivas futuras

Paulo Henrique Rosado de Castro, MD, PhD, MBA

Conflitos de interesse

- Declaro não ter conflitos de interesse.

Afiliações



Universidade Federal do Rio de Janeiro

- Chefe do Serviço de Medicina Nuclear e Coordenador da Residência Médica em Medicina Nuclear, Hospital Universitário Clementino Fraga Filho
- Professor adjunto, Instituto de Ciências Biomédicas
- Professor permanente, PPG em Medicina (Radiologia), Fac. Medicina



Instituto D'Or de Pesquisa e Ensino

- Professor colaborador, Doutorado em Ciências Médicas



Sociedade Brasileira de Medicina Nuclear

- Diretor Científico

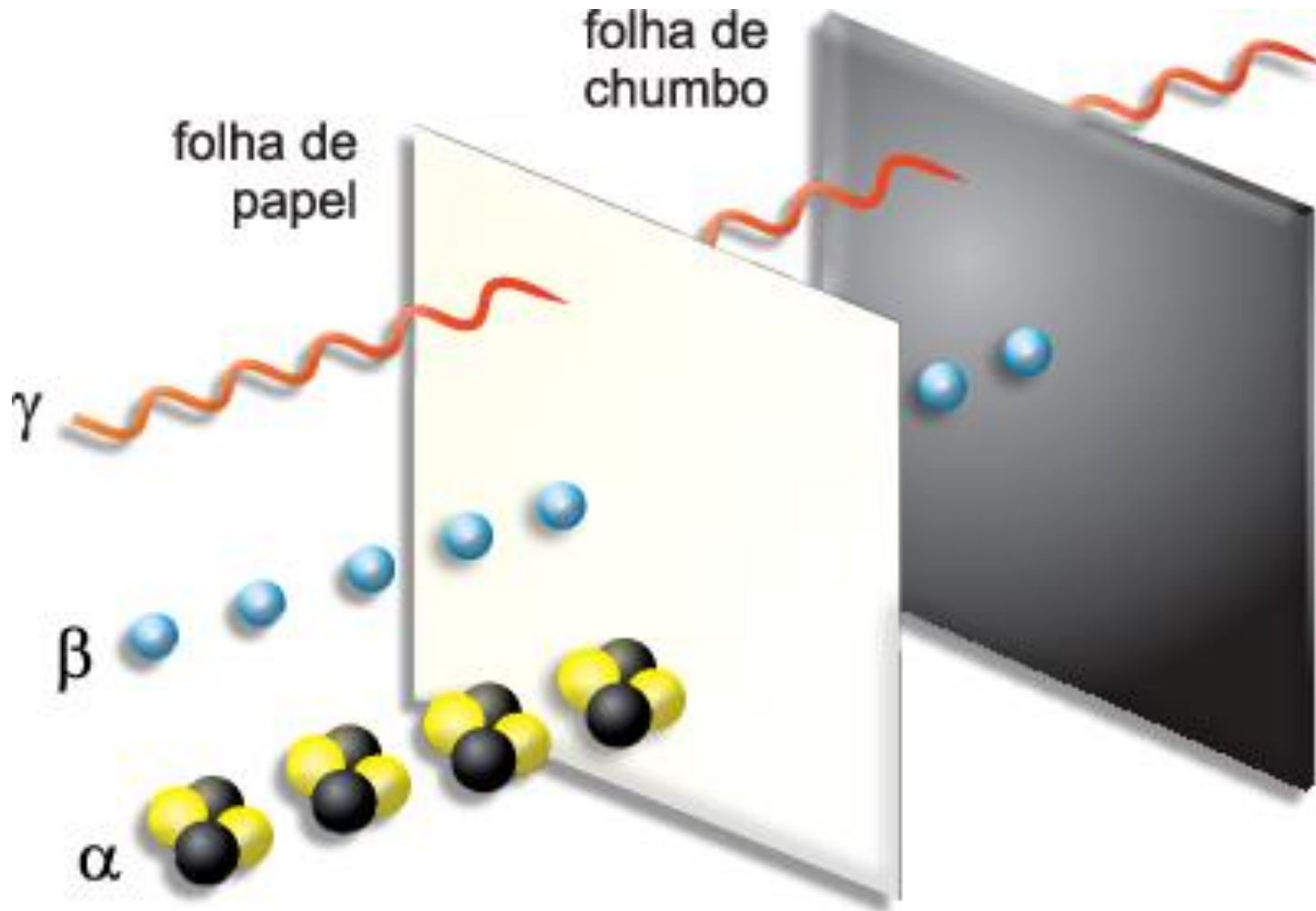
Sumário

- Introdução
- Pares teranósticos
- Teranóstico em oncologia
- Conclusão
- Perspectivas

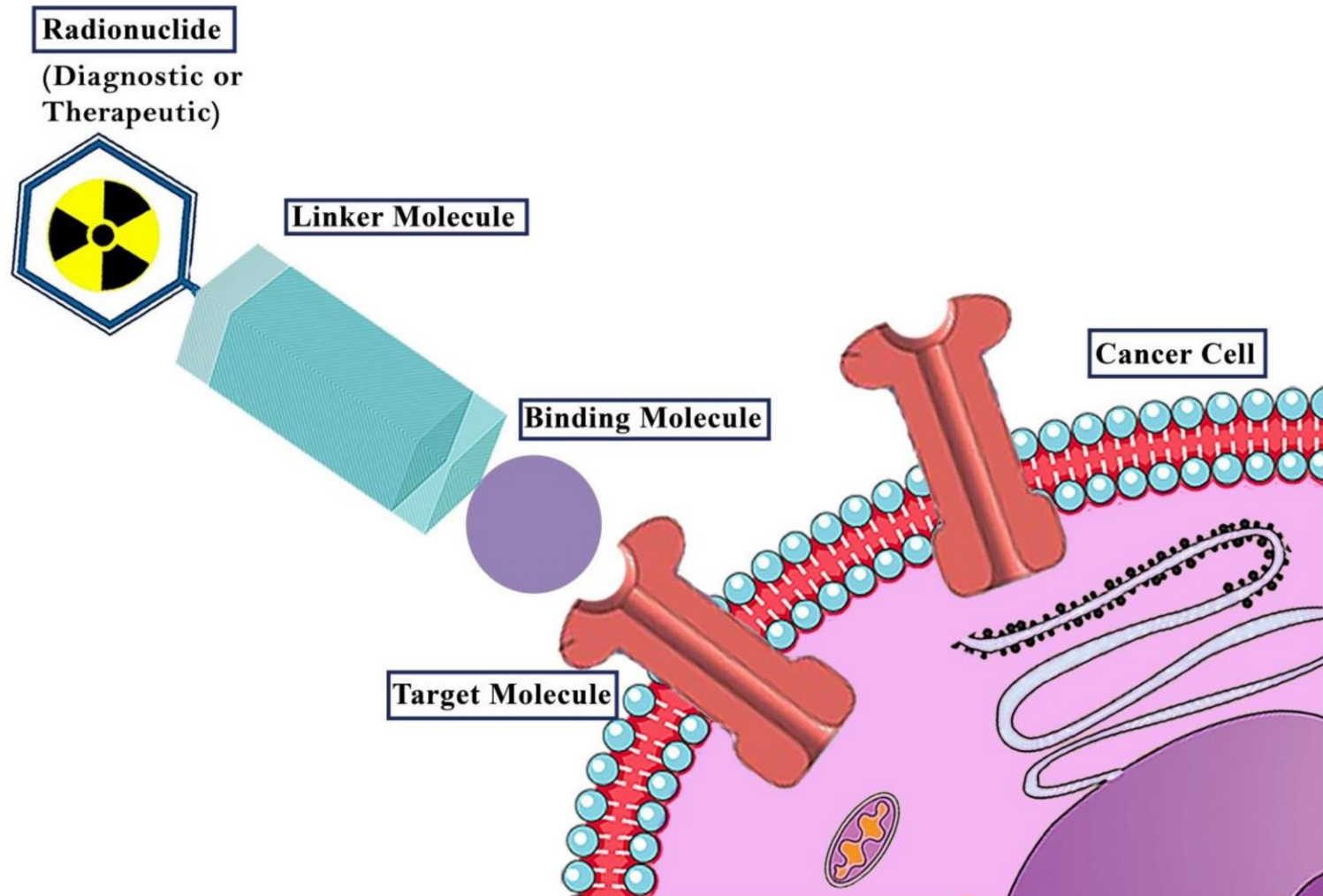
Introdução



Introdução



Introdução



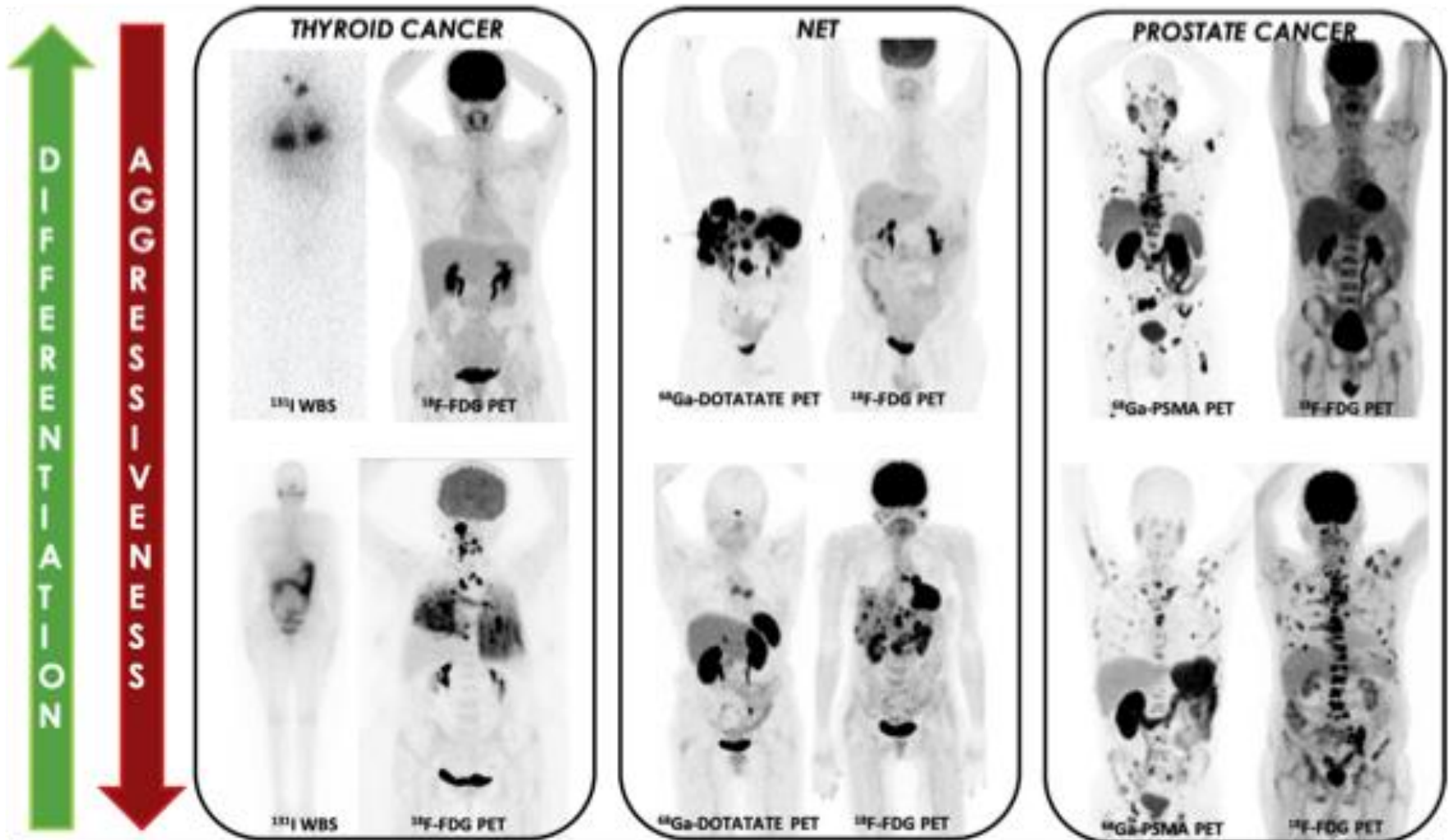
Introdução

General Concepts in Theranostics



Rafael F. Nunes, MD^{a,*}, Roberta M.F. Zuppani, MD^b, Artur M. Coutinho, MD, PhD^{a,b},
Felipe G. Barbosa, MD^a, Marcelo T. Sapienza, MD, PhD^b, Jose Flavio G. Marin, MD^{a,b},
Carlos A. Buchpiguel, MD, PhD^{a,b}

Introdução

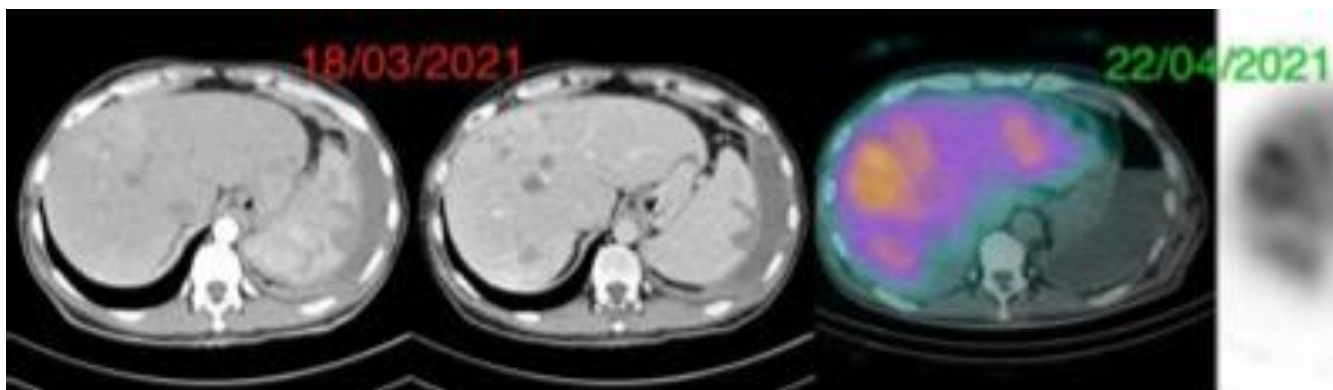
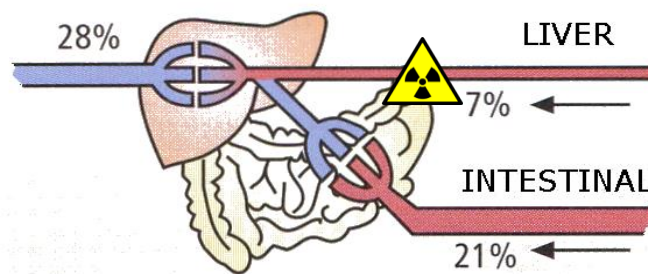
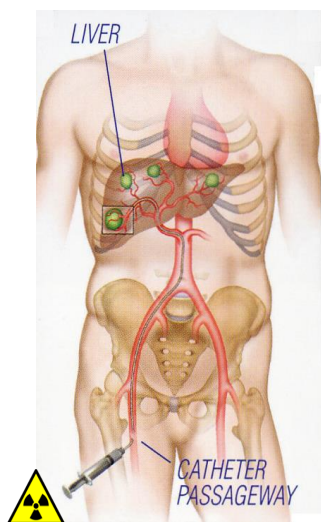


Pares teranósticos atuais

Alvo	Doença	Diagnóstico	Terapia
Simporte sódio-iodo	Hipertireoidismo Câncer de tireoide	123I 99mTc-O4-	131I
Transportador norepinefrina	Neuroblastoma Feocromocitoma	mIBG-123I	mIBG-131I
Hidroxiapatita nos ossos	Câncer de próstata	MDP-99mTc Fluoreto-18F	223Ra
Receptores de somatostatina	Tumores neuroendócrinos	DOTA-68Ga Octreo-111In/99mTc	octreotato-177Lu/90Y
PSMA	Câncer de próstata	PSMA-68Ga/18F	PSMA-177Lu/225Ac
Microvasculatura hepática	Carcinoma hepatocelular Colangiocarcinoma Metástases hepáticas	MAA-99mTc	microsferas-90Y
CD20 (antígeno em linfócitos B)	Linfoma não-Hodgkin	Imunohistoquímica anti-CD20	anti-CD20-131I/90Y

Aplicações teranósticas

Terapia de lesões hepáticas com microesferas radioativas marcadas com ^{90}Y



Aplicações teranósticas

Braquiterapia com Rênio-188 para tumores de pele de difícil ressecção cirúrgica



Pares teranósticos em investigação

Alvo	Doença	Diagnóstico	Terapia
Receptor CXCR4	Múltiplos tipos de câncer, incluindo mieloma múltiplo, linfomas, leucemias, glioblastoma, de pâncreas, melanoma e de próstata	Liigante CXCR4-68Ga	CXCR4-177Lu
PD1/PD-L1	Múltiplos tipos de câncer, incluindo de pulmão, melanoma, renal e linfomas	Anti-PD1-PD-L1-89Zr/18F	Inibidores de checkpoint anti-PD1-PD-L1-89Zr/18F
HER2	Câncer de mama	Anti-HER2-89Zr	Inibidores de HER2
Proteína de ativação de fibroblastos	Múltiplos tipos de câncer, incluindo de pâncreas, sarcoma, pulmão, melanoma, renal e linfomas	Inibidor da proteína de ativação de fibroblastos-68Ga (FAPI-04)	90Y-FAPI-04

Tumores neuroendócrinos

DOTATATE-Lutécio-177

The NEW ENGLAND JOURNAL of MEDICINE

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, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajakanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

Tumores neuroendócrinos

DOTATATE-Lutécio-177

- Pacientes com tumores neuroendócrinos avançados do intestino médio
 - progressão da doença durante a terapia com análogos de somatostatina
 - opções terapêuticas limitadas.

Tumores neuroendócrinos

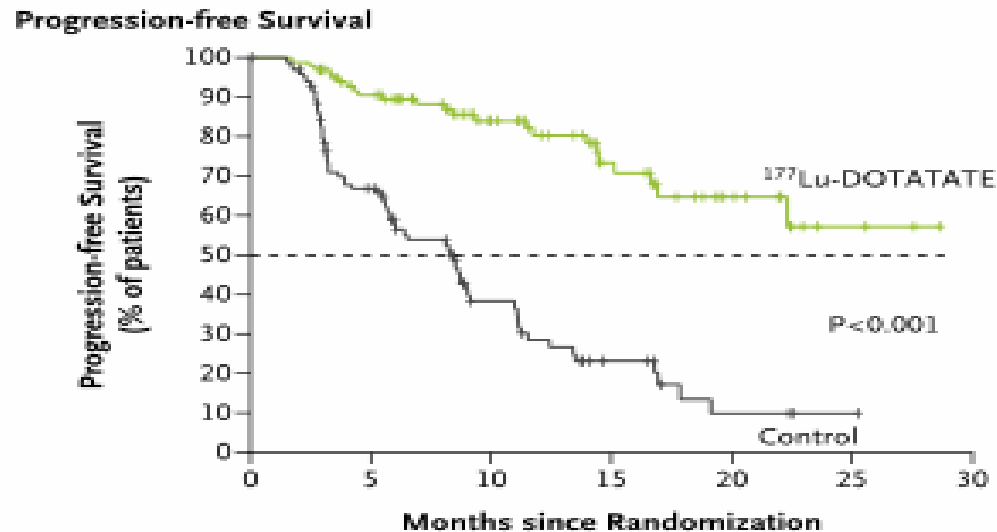
DOTATATE-Lutécio-177

- 229 pacientes com tumores neuroendócrinos metastáticos
 - 116 pacientes receberam 1 dose de DOTATATE-¹⁷⁷Lu a cada 8 semanas
 - 4 infusões intravenosas e octreotida LAR 30 mg
 - 113 pacientes no grupo controle
 - octreotida LAR 60 mg a cada 4 semanas

Tumores neuroendócrinos

DOTATATE-Lutécio-177

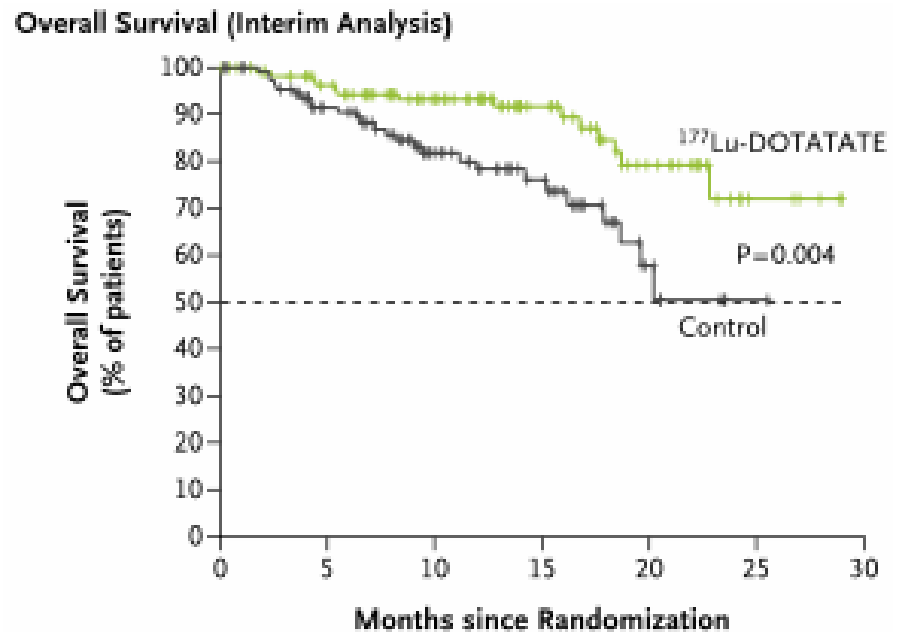
- Sobrevida livre de progressão no 20º mês:
 - 65,2% (IC, 50,0 a 76,8) no grupo DOTATATE-¹⁷⁷Lu.
 - 10,8% (95% CI, 3,5 a 23,0) no grupo de controle.



Tumores neuroendócrinos

DOTATATE-Lutécio-177

- Análise provisória da sobrevida global
 - 14 óbitos no grupo DOTATATE-¹⁷⁷Lu
 - 26 no grupo controle

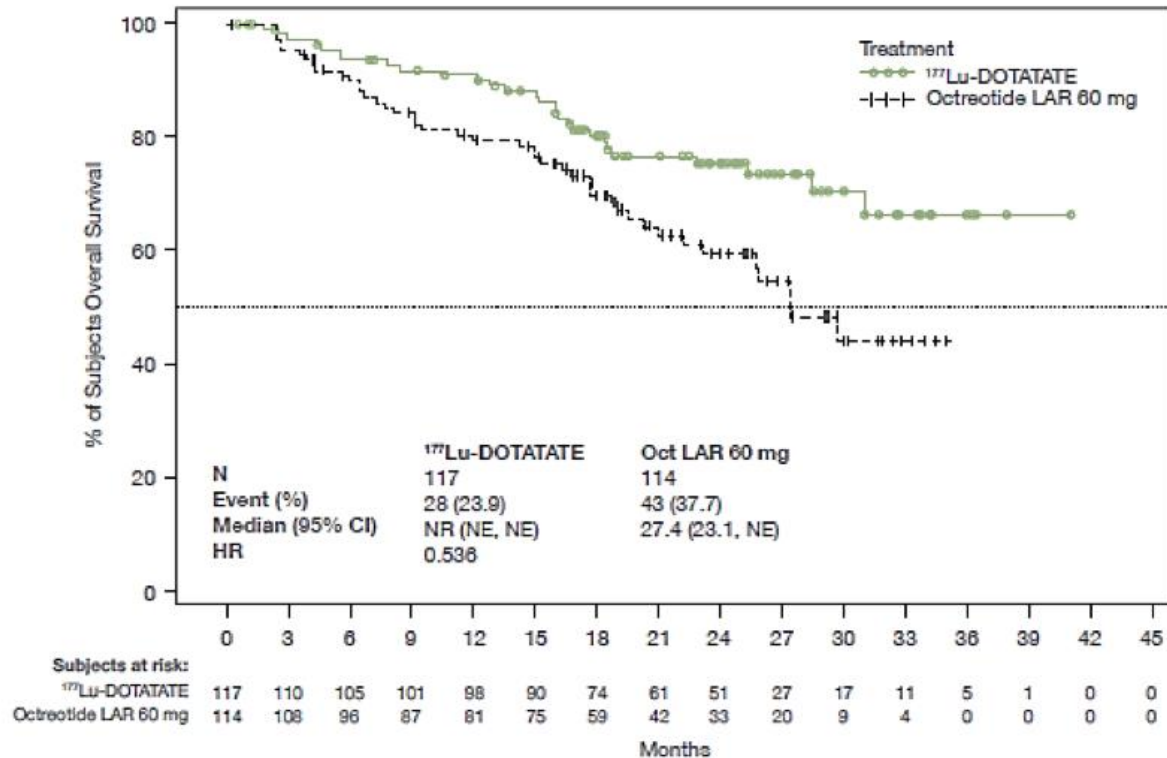


Tumores neuroendócrinos

DOTATATE-Lutécio-177

Overall Survival

- At this first update, median OS was 27.4 months in Oct arm and still not reached in ¹⁷⁷Lu arm



Cutoff date 30 June 2016

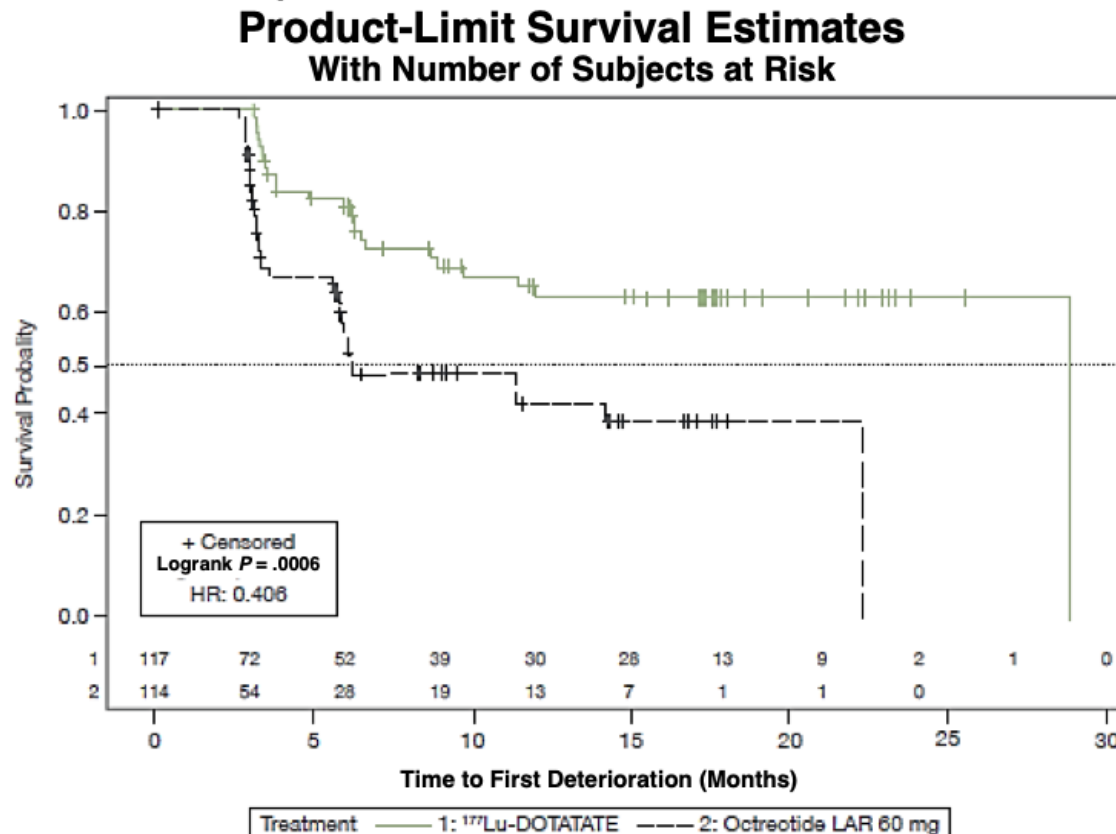
Strosberg J, et al. *J Clin Oncol*. 2018;36(suppl): Abstract 4099.

Tumores neuroendócrinos

DOTATATE-Lutécio-177

Global Health Status TTD

- HRQoL TTD was significantly longer in the ^{177}Lu arm vs the Oct arm for global health status (HR: 0.406; $P = .0006$)



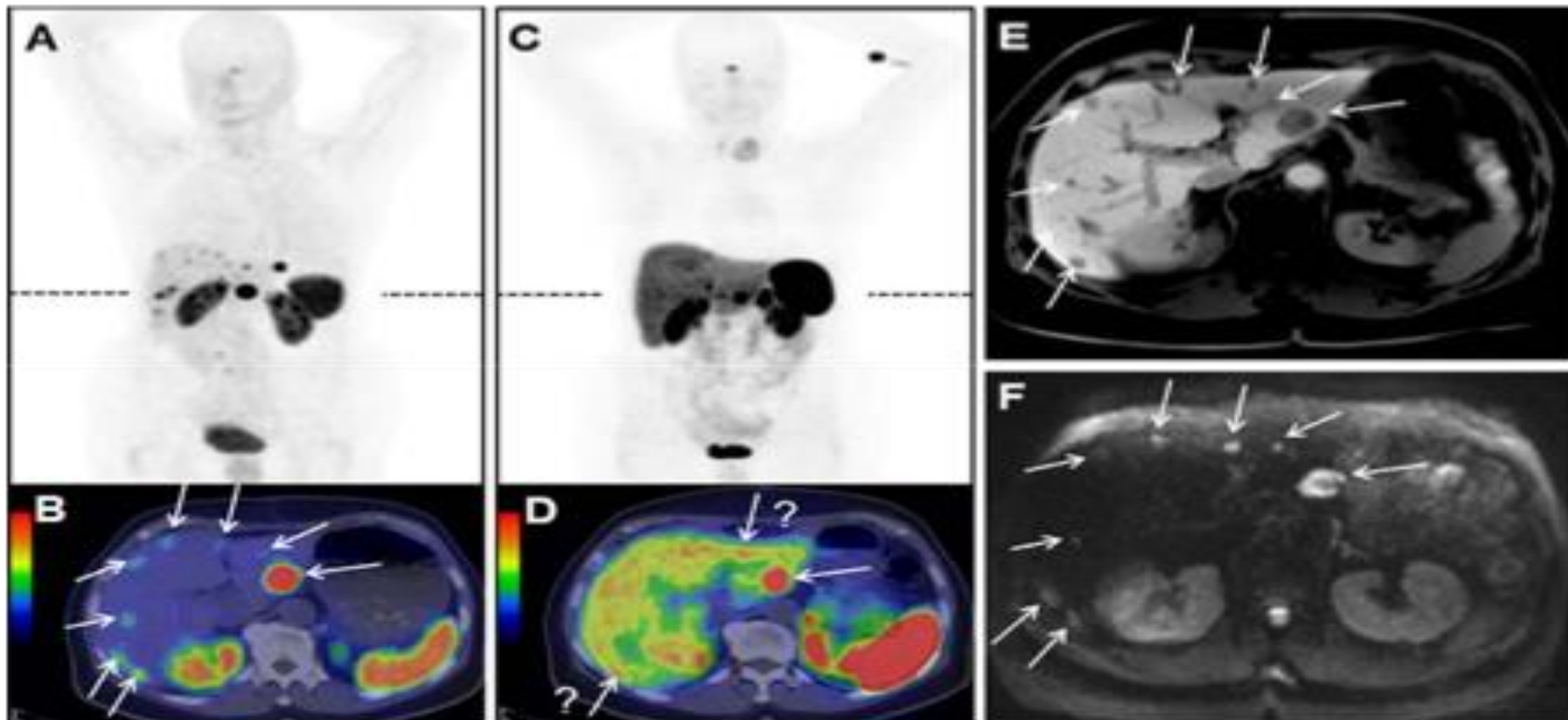
Tumores neuroendócrinos

DOTATATE-Lutécio-177

- Após seguimento médio de 6,3 anos:
 - Melhora da sobrevida livre de progressão
 - Melhora da sobrevida global mediana 48,0 vs 36,3

Tumores neuroendócrinos

- Novos radiofármacos - antagonistas



Câncer de próstata

Rádio-223

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JULY 18, 2013

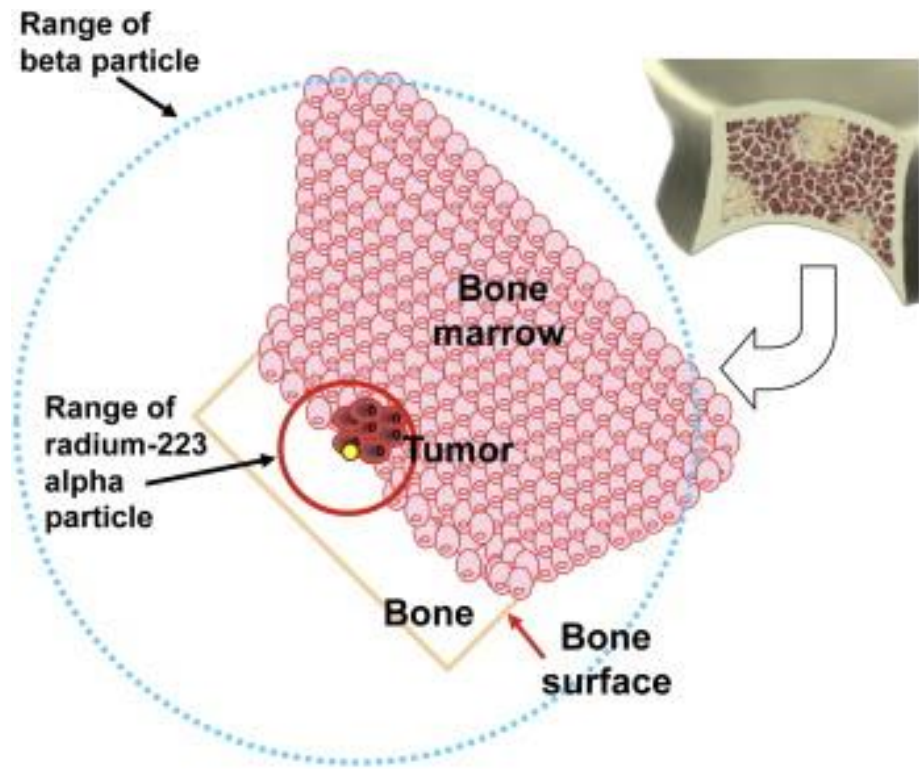
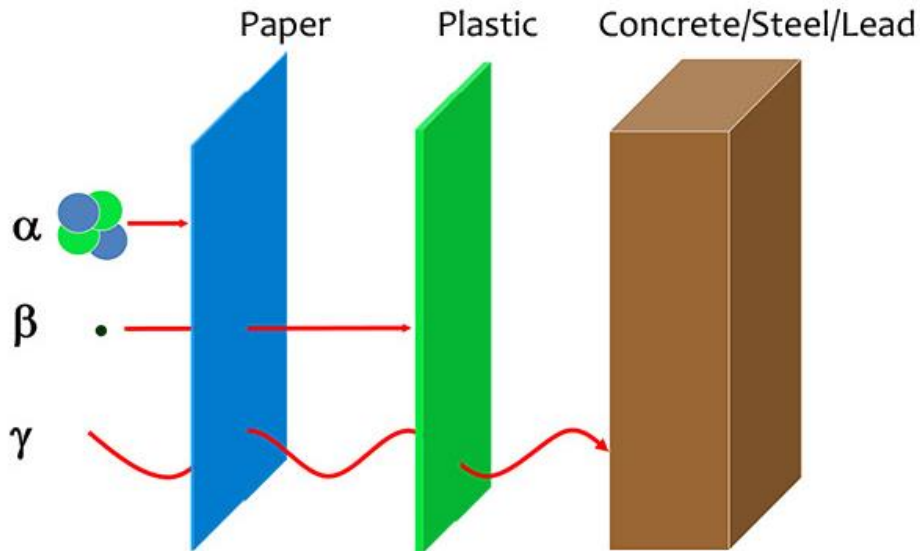
VOL. 369 NO. 3

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. Fosså, 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*

Câncer de próstata

Rádio-223



Câncer de próstata

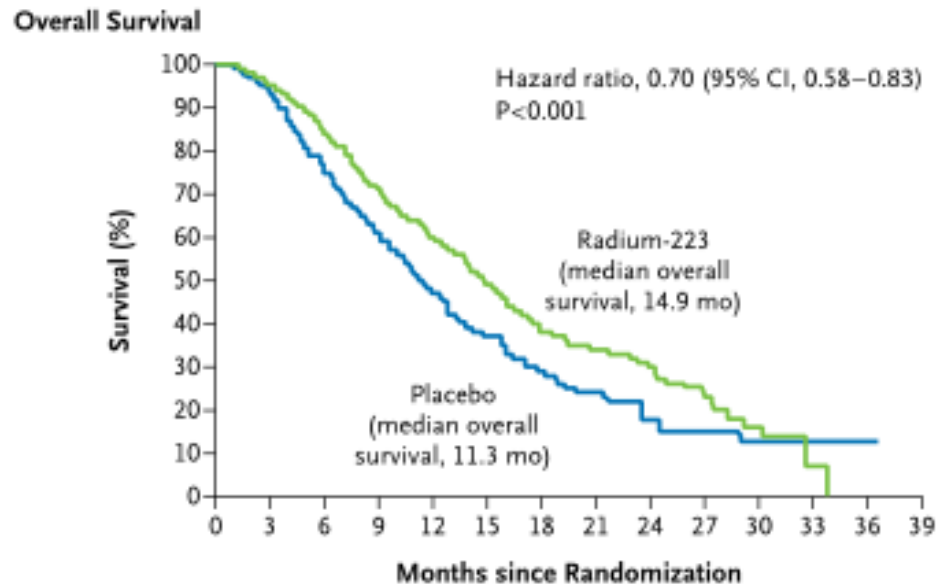
Rádio-223

- Fase 3
- CPmRC
- Randomizado, duplo-cego, placebo controlado
- 921 pacientes, 2:1
- Não receberam, não eram elegíveis ou recusaram docetaxel
- 6 injeções de cloreto de rádio-223 ou placebo

Câncer de próstata

Rádio-223

- Desfecho primário: maior sobrevida global (mediana 14,9 meses vs. 11,3 meses)



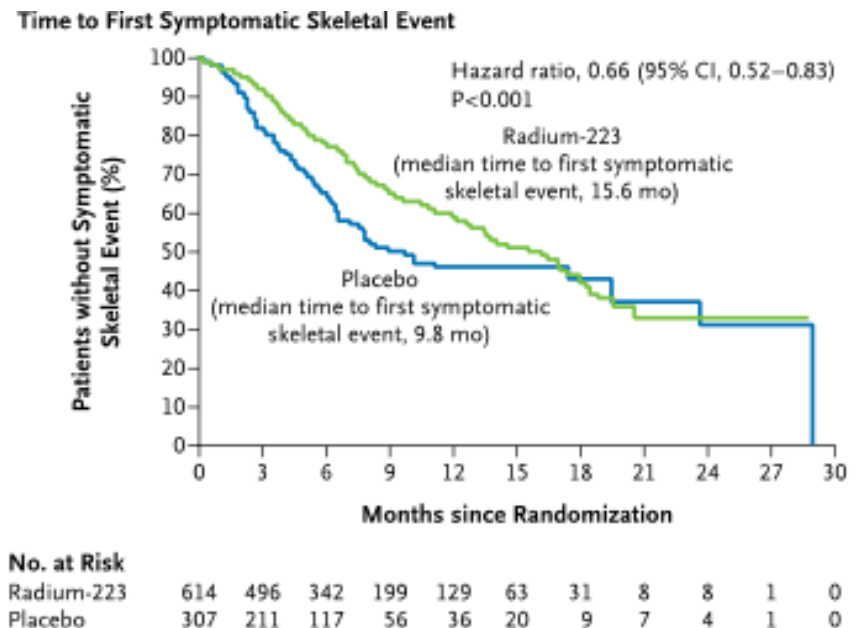
Parker et al. N Engl J Med 2013

No. at Risk														
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

Câncer de próstata

Rádio-223

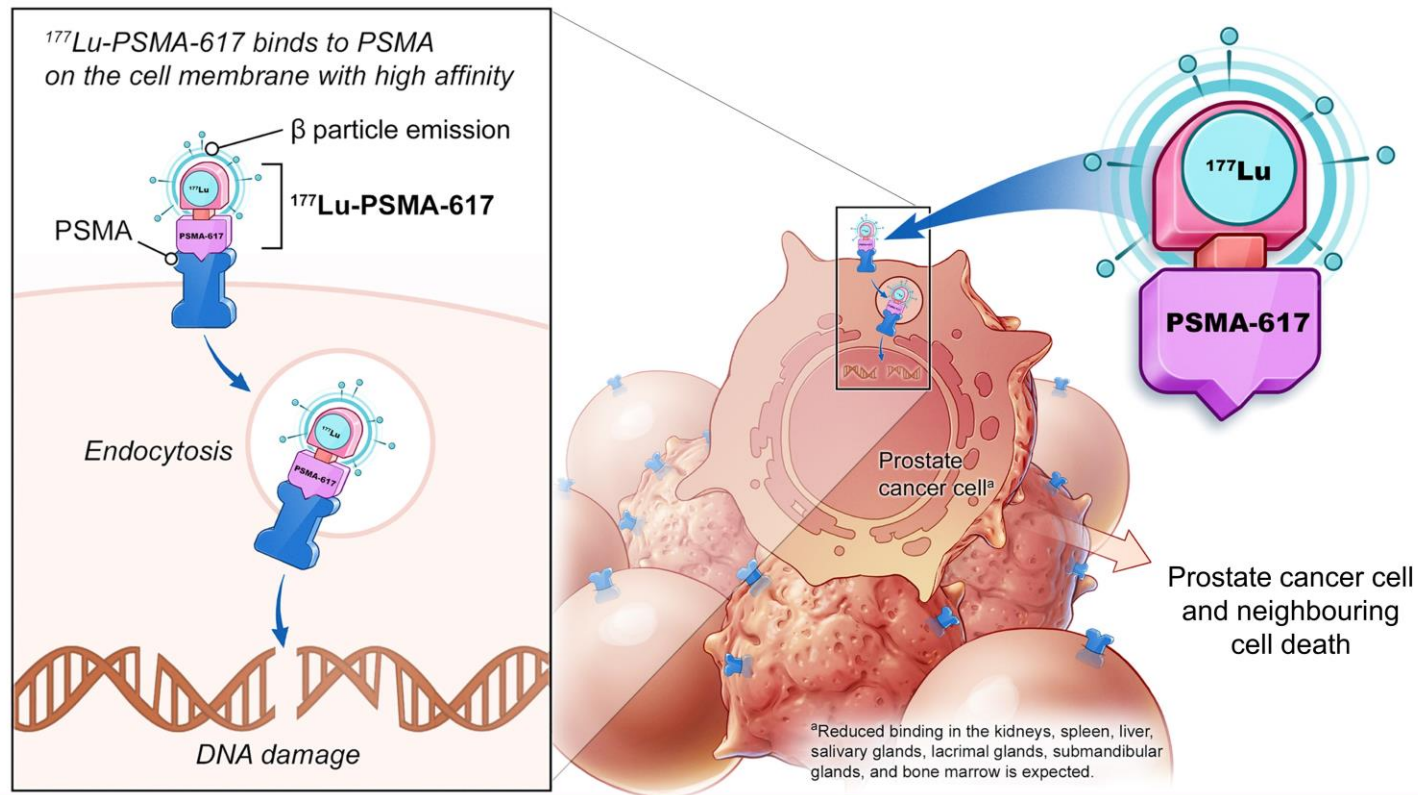
- Desfecho secundário:
 - Tempo para primeiro evento ósseo sintomático
 - 15,6 vs. 9,8 meses



Câncer de próstata

PSMA-lutécio-177

¹⁷⁷Lu-PSMA-617 targeted radioligand therapy



Câncer de próstata

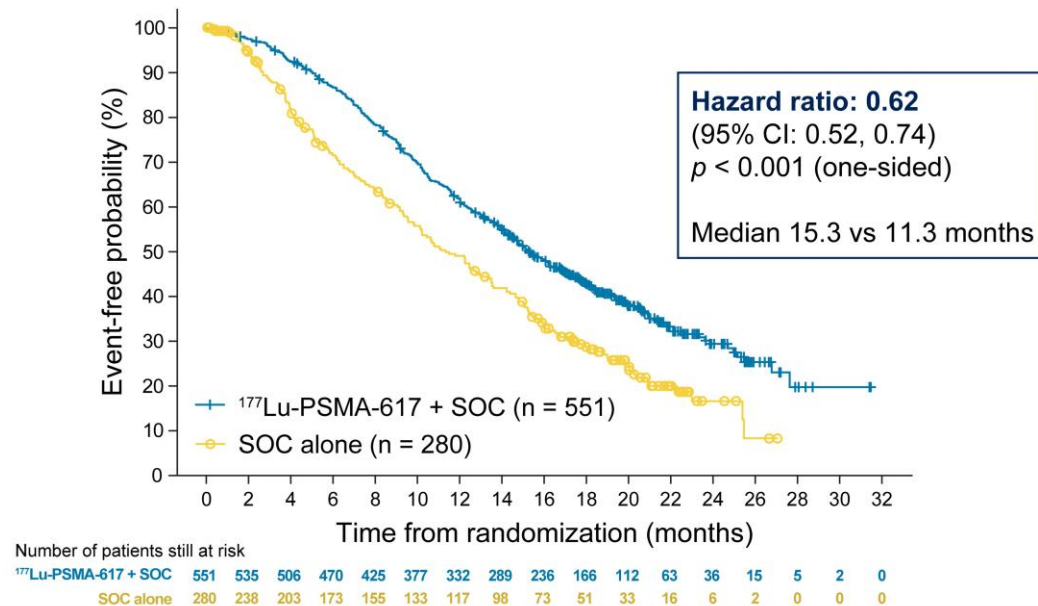
PSMA-lutécio-177

16

Primary endpoints: ^{177}Lu -PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



Presented By: Michael J. Morris

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2021 ASCO
ANNUAL MEETING

Câncer de próstata PSMA-lutécio-177

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

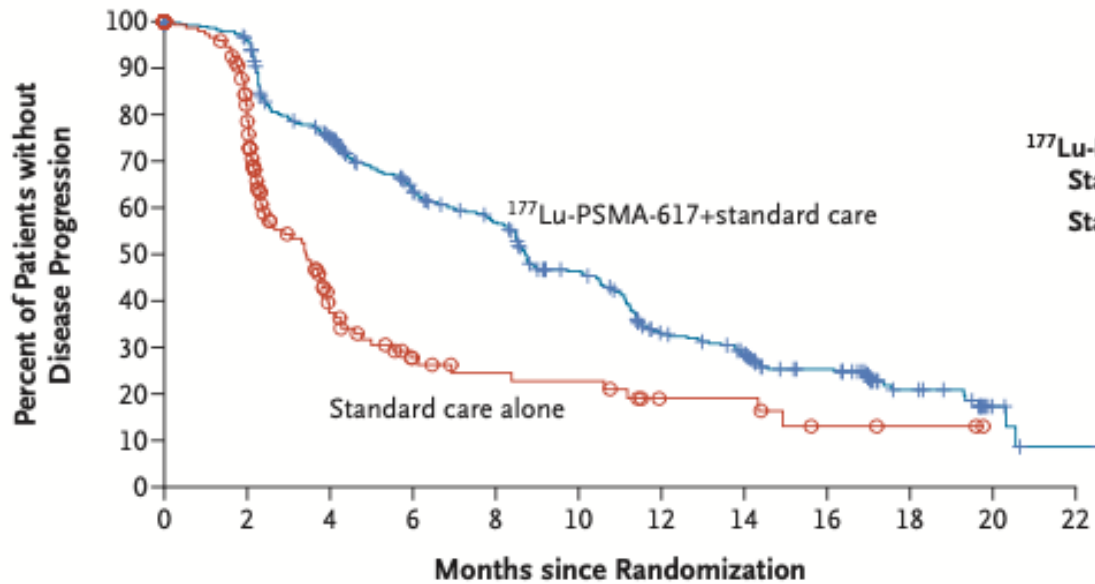
Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

Câncer de próstata

PSMA-lutécio-177

A Imaging-Based Progression-free Survival

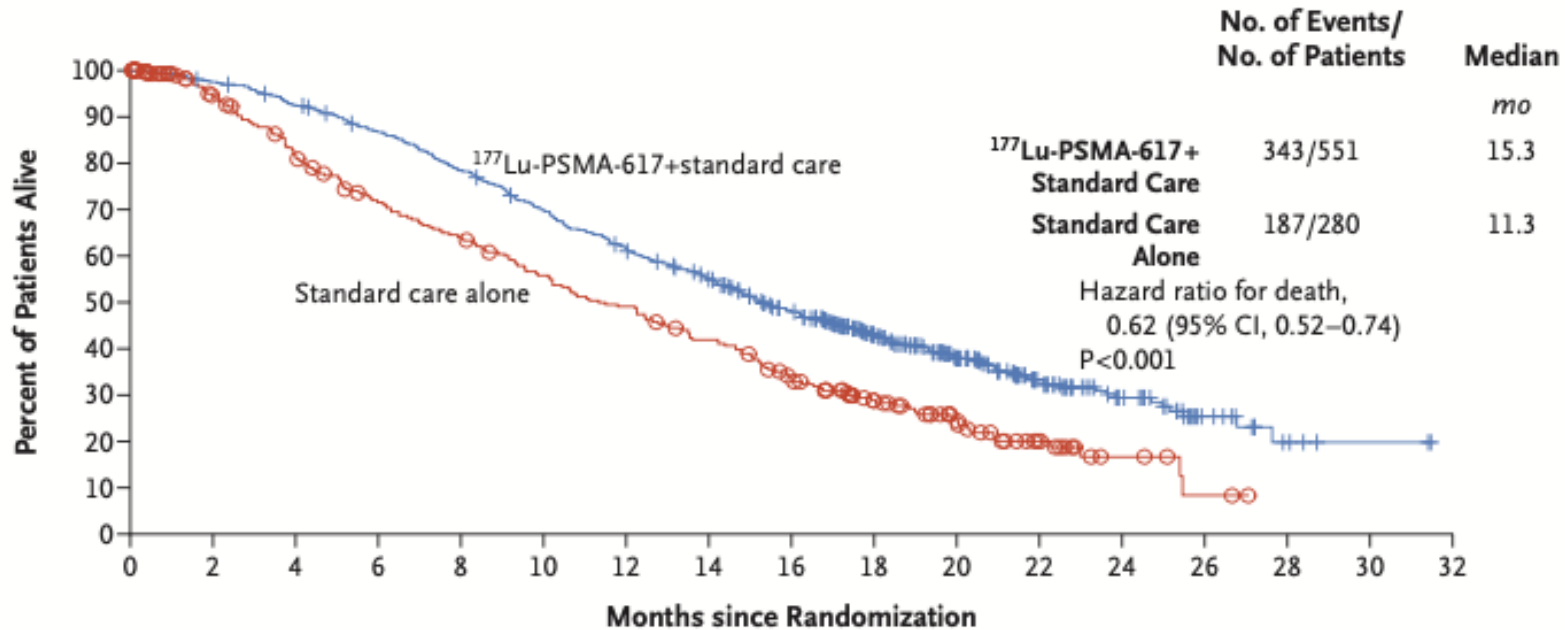


No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22
¹⁷⁷ Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

Câncer de próstata PSMA-lutécio-177

B Overall Survival

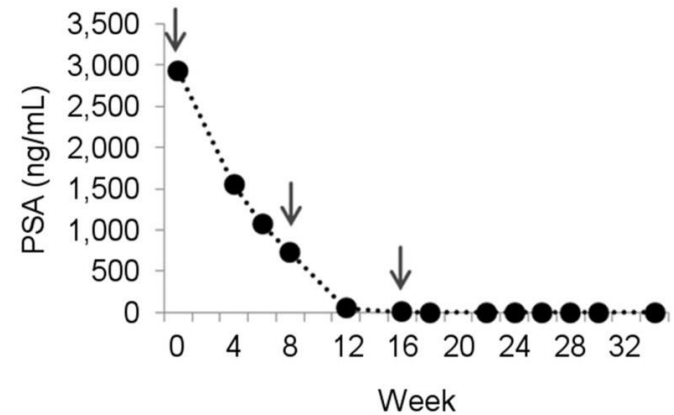
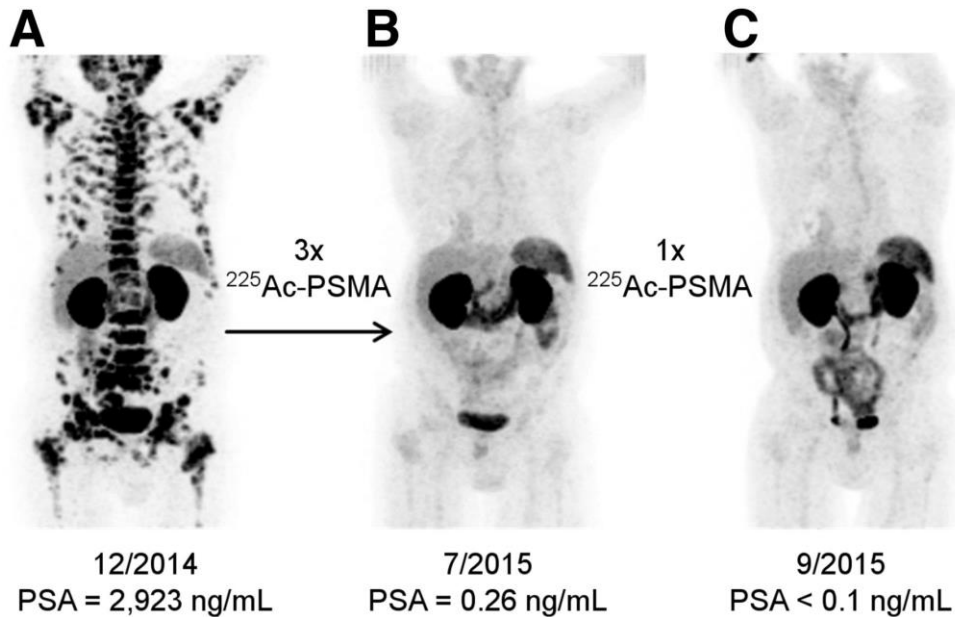


No. at Risk

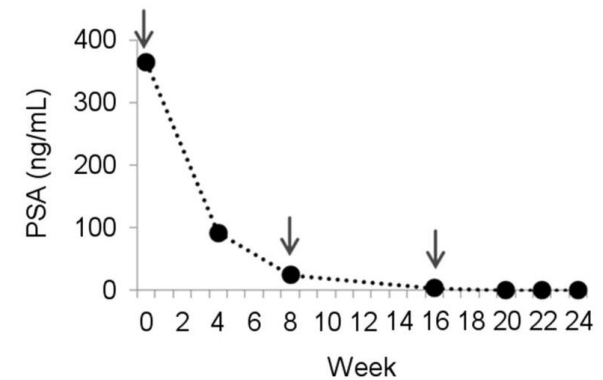
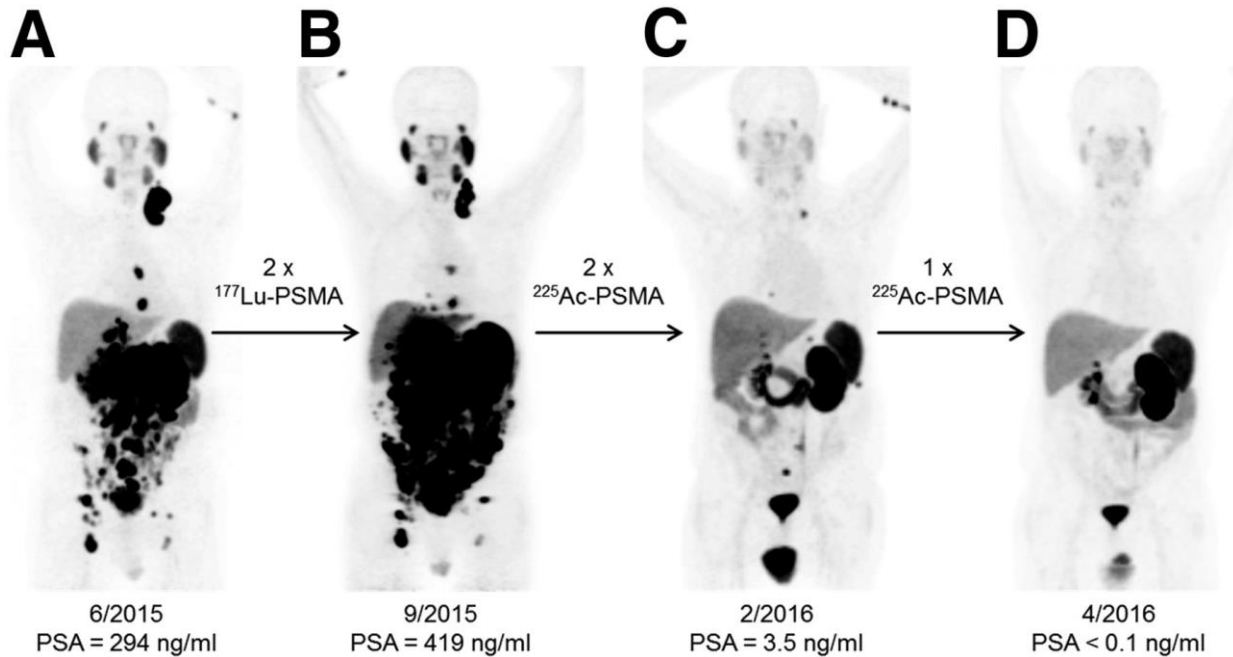
¹⁷⁷ Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Câncer de próstata

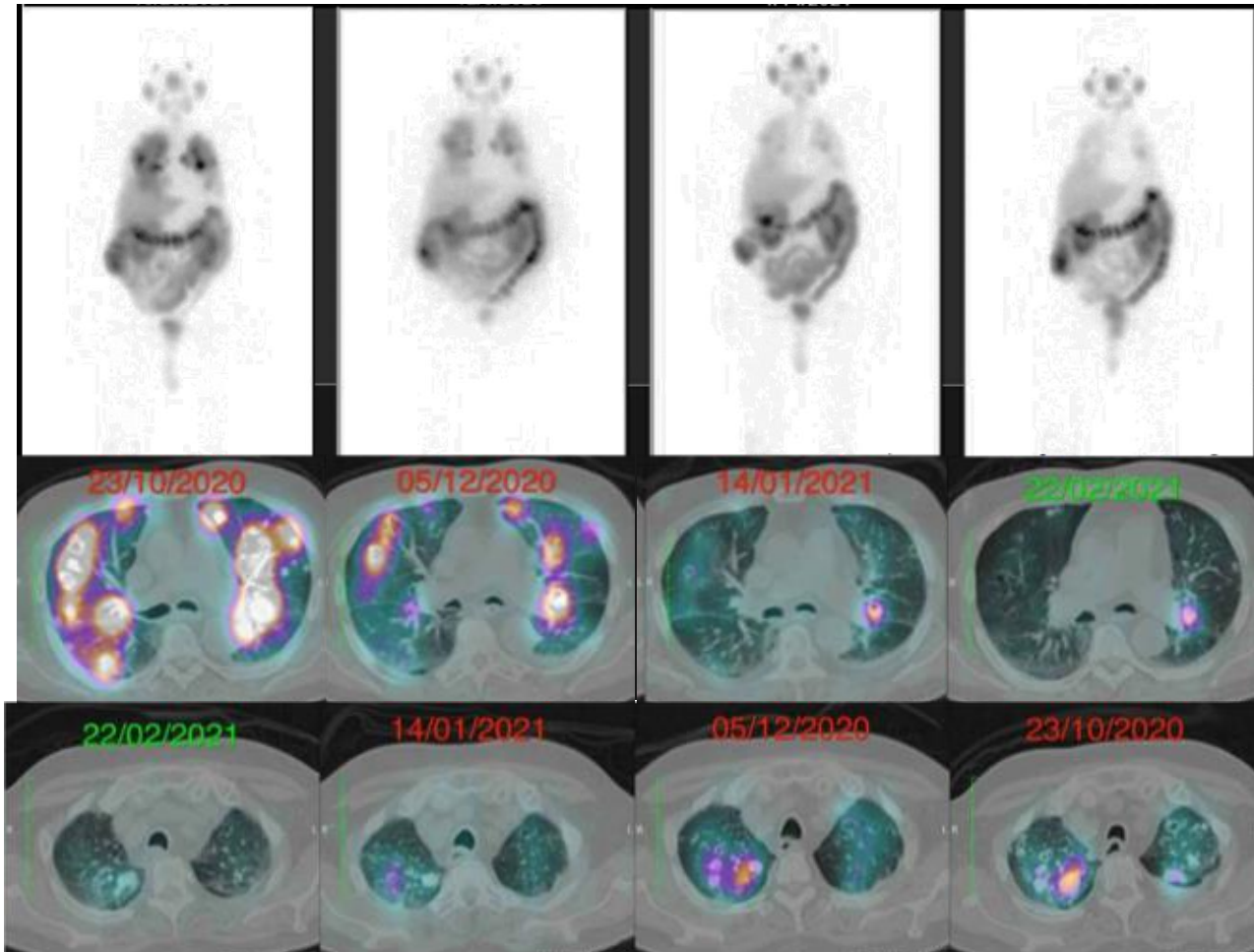
PSMA-actínio-225



Câncer de próstata PSMA-actínio-225

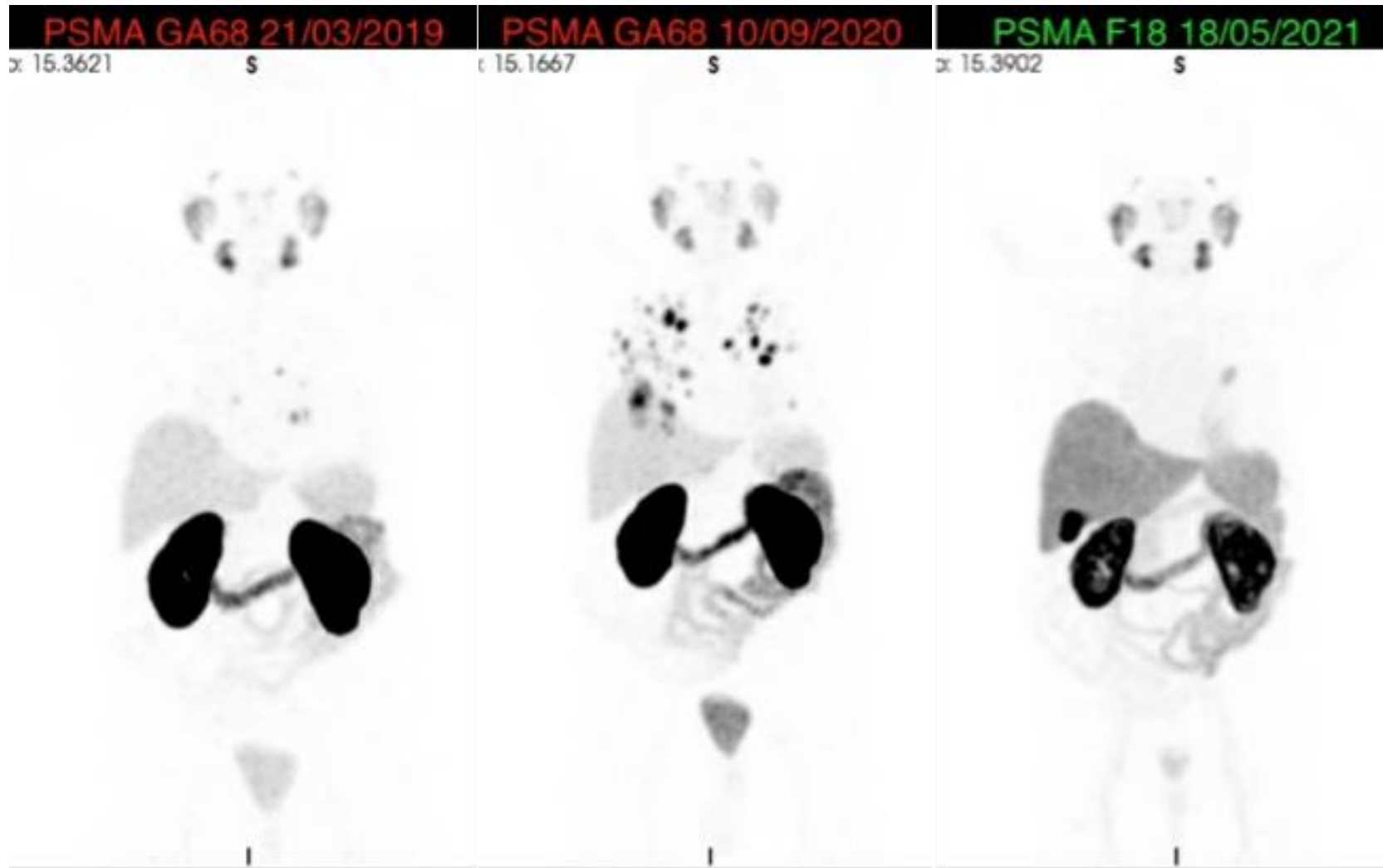


Câncer de próstata PSMA-lutécio-177



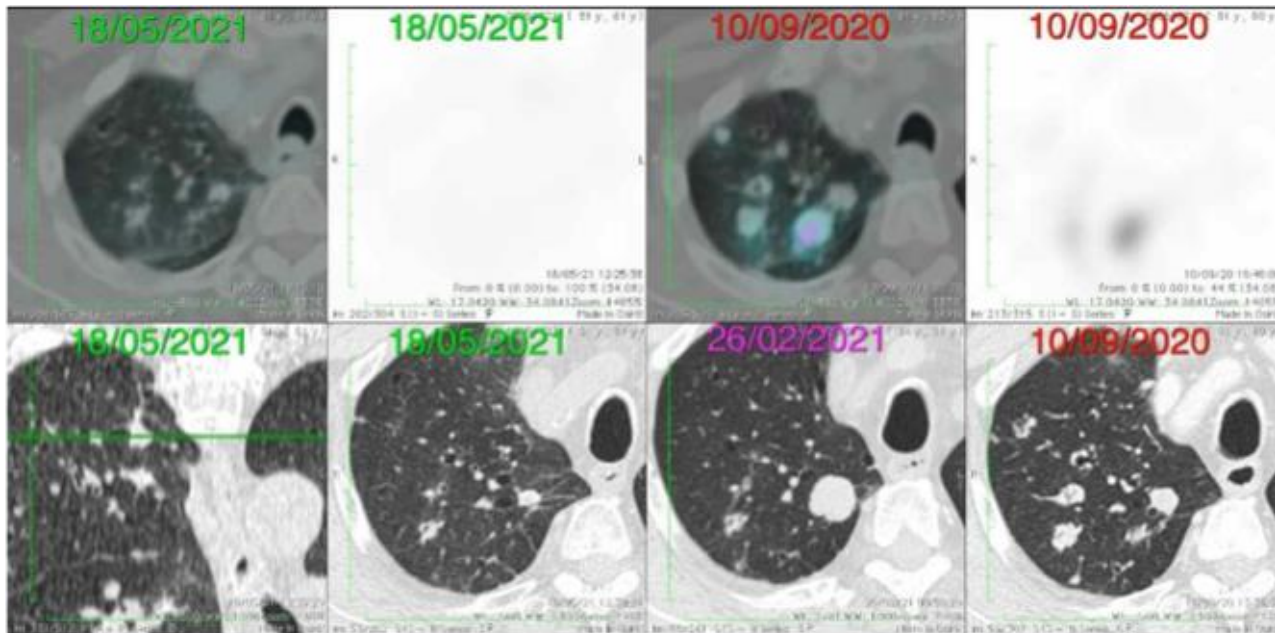
Câncer de próstata

PSMA-lutécio-177



Câncer de próstata

PSMA-lutécio-177



Heterogeneidade



Mol Imaging Biol (2018)
DOI: 10.1007/s11307-018-1252-5
© World Molecular Imaging Society, 2018



RESEARCH ARTICLE

Pre-therapy Somatostatin Receptor-Based Heterogeneity Predicts Overall Survival in Pancreatic Neuroendocrine Tumor Patients Undergoing Peptide Receptor Radionuclide Therapy

Rudolf A. Werner,^{1,2} Harun Ilhan,³ Sebastian Lehner,^{3,4} László Papp,⁵ Norbert Zsótér,⁶ Imke Schatka,⁷ Dirk O. Muegge,² Mehrbod S. Javadi,¹ Takahiro Higuchi,^{2,8} Andreas K. Buck,² Peter Bartenstein,³ Frank Bengel,⁹ Markus Essler,¹⁰ Constantin Lapa,² Ralph A. Bundschuh¹⁰

European Journal of Nuclear Medicine and Molecular Imaging
<https://doi.org/10.1007/s00259-019-04439-9>

ORIGINAL ARTICLE

Prognostic Significance of Somatostatin Receptor Heterogeneity in Progressive Neuroendocrine Tumor Treated with Lu-177 DOTATOC or Lu-177 DOTATATE

Josephine Graf¹ & Ulrich-Frank Pape² & Henning Jann² & Timm Denecke³ & Ruza Arsenic⁴ & Winfried Brenner¹ & Marianne Pavel^{2,5} & Vikas Prasad^{1,6} 

Received: 28 December 2018 / Accepted: 11 July 2019
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Heterogeneidade

Assessment of Quality of SSTR⁽⁶⁾ expression:

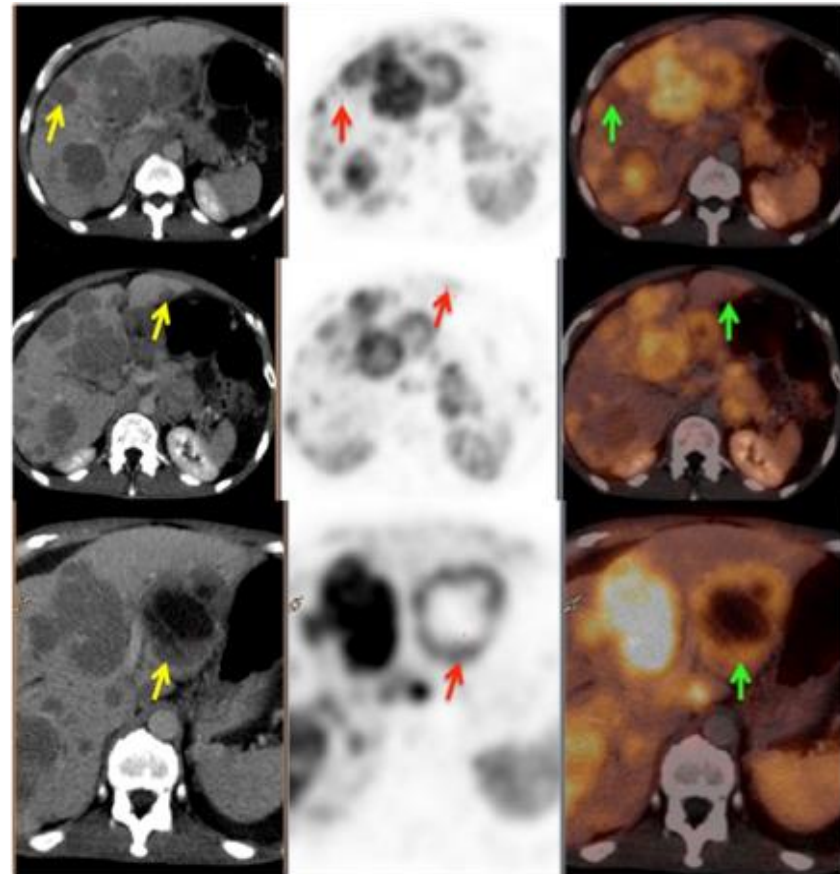
- Index lesions: Lesions greater than 2 cm and definitely visible on Baseline PET/CT image
- $\geq 50\%$ heterogeneous target lesions = patient with heterogeneous expression
- $< 50\%$ target lesions heterogeneous = patient with homogeneous expression

Homogeneous receptor expression

35 (55.6%) Patients
median TTP⁽⁷⁾: 54 months
median OS⁽⁸⁾: not reached

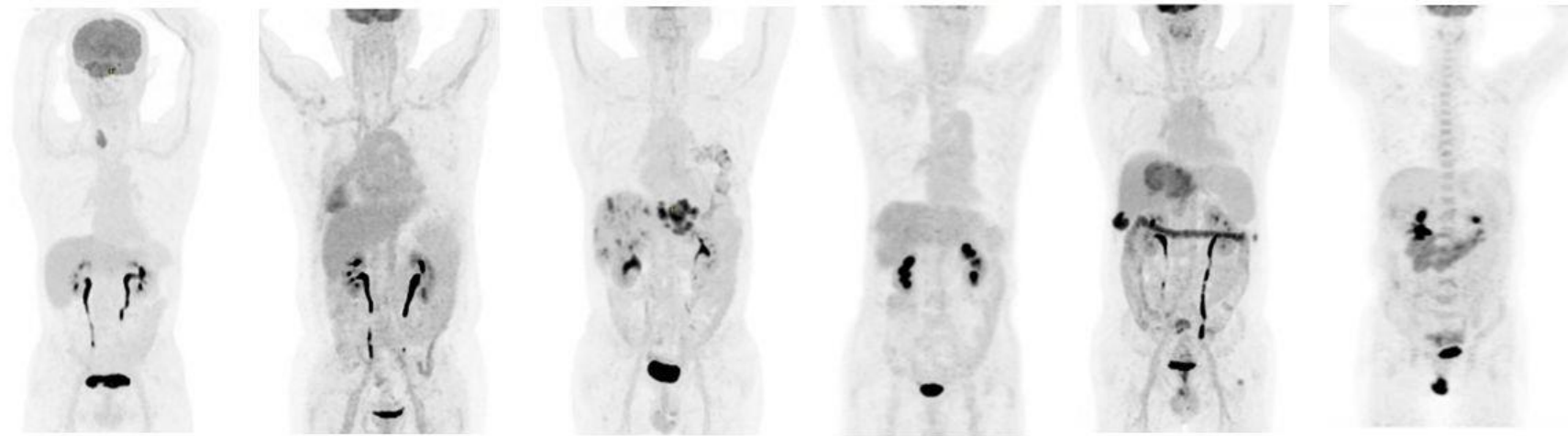
Heterogeneous receptor expression

28 (44.4%) Patients
median TTP: 26 months
median OS: not reached

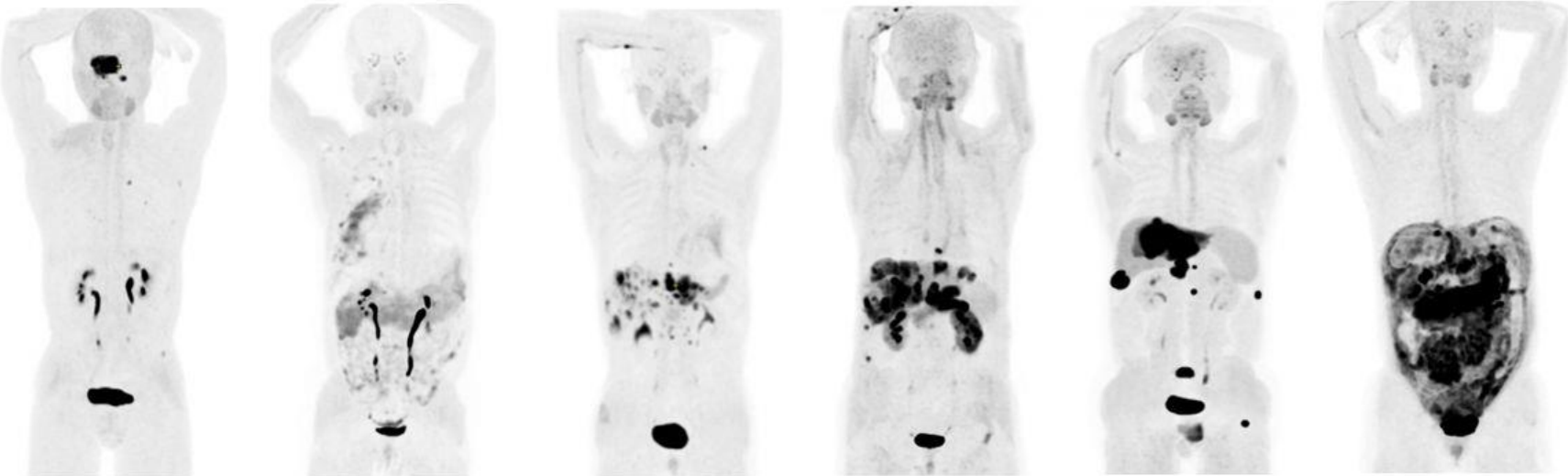


Perspectivas

¹⁸F-FDG



⁶⁸Ga-FAPI



Nasopharyngeal cancer

Lung cancer

Gastric cancer

Pancreatic cancer

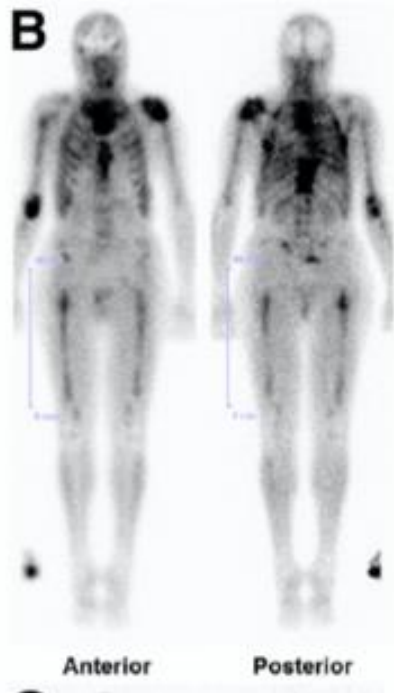
Liver cancer

Ovarian cancer

Perspectivas

FEATURED ARTICLE OF THE MONTH

**Feasibility, Biodistribution, and Preliminary Dosimetry
in Peptide-Targeted Radionuclide Therapy of Diverse
Adenocarcinomas Using ^{177}Lu -FAP-2286:
First-in-Humans Results**

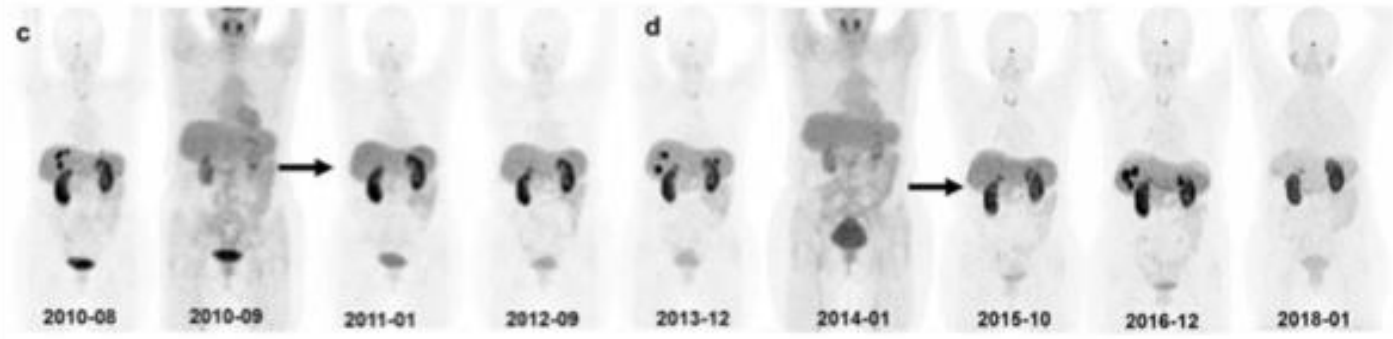
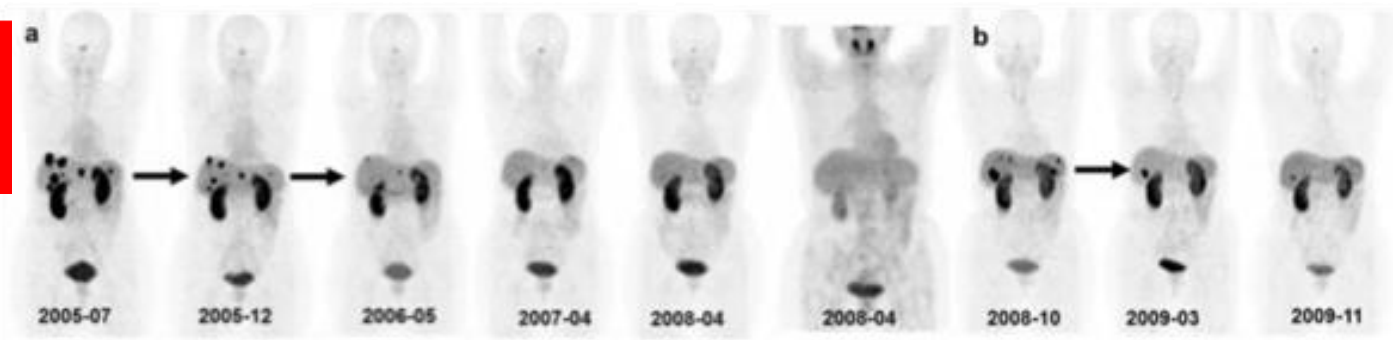


PET FAP antes

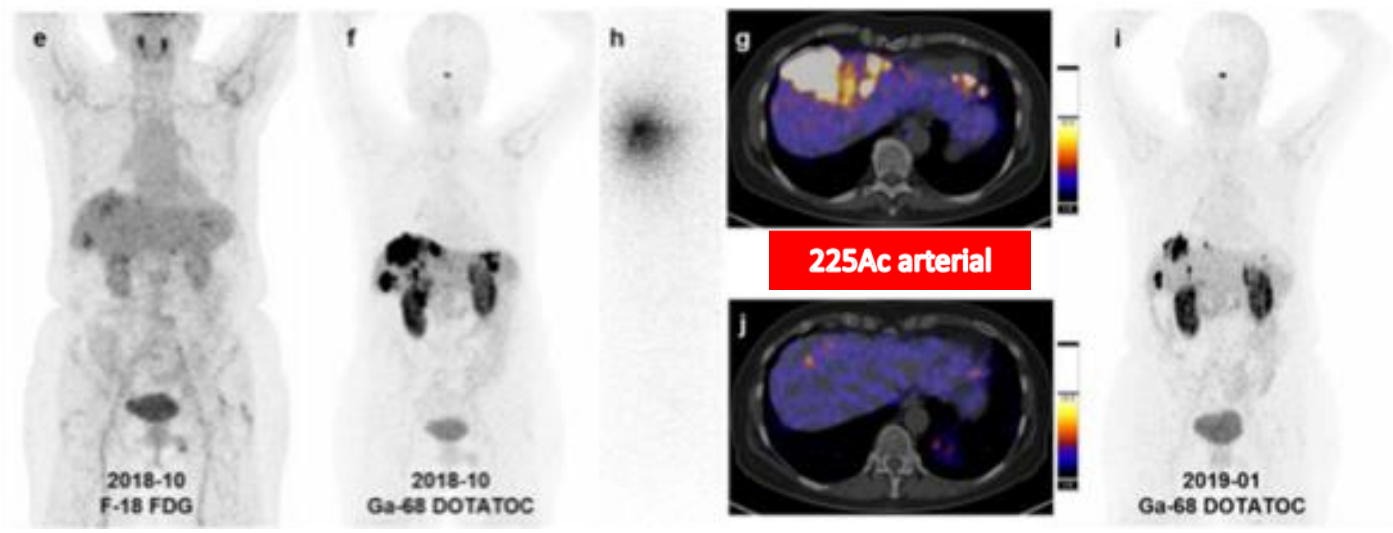


PET FAP após 8
semanas

2012-2014
8 ciclos de
90Y e 177Lu
(DUO-PRRT)




2017
relaparotomia,
termoablação por
radiofrequência e
quimioembolização
transarterial



225Ac arterial

Study of RYZ101 Compared With SOC in Pts w Inoperable SSTR+ Well-differentiated GEP-NET That Has Progressed Following 177Lu-SSA Therapy (ACTION-1)

ClinicalTrials.gov Identifier: NCT05477576

 The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

[Recruitment Status](#) ⓘ : Recruiting

[First Posted](#) ⓘ : July 28, 2022

[Last Update Posted](#) ⓘ : August 21, 2023

See [Contacts and Locations](#)

[View this study on the modernized ClinicalTrials.gov](#)

Sponsor:

Condition or disease ⓘ	Intervention/treatment ⓘ	Phase ⓘ
GEP-NET Gastroenteropancreatic Neuroendocrine Tumor Gastroenteropancreatic Neuroendocrine Tumor Disease Neuroendocrine Tumors Carcinoid Carcinoid Tumor Pancreatic NET	Drug: RYZ101 Drug: Everolimus 10 mg Drug: Sunitinib 37.5 MG Drug: Octreotide LAR 60 MG Injection Drug: Lanreotide 120Mg Sa Susp Inj Syringe	Phase 3

Study Design

Go to

Study Type ⓘ : Interventional (Clinical Trial)

Estimated Enrollment ⓘ : 218 participants

Allocation: Randomized

Intervention Model: Parallel Assignment

Intervention Model Description: This study aims to determine the safety, pharmacokinetics (PK) and recommended Phase 3 dose (RP3D) of RYZ101 in Part 1, and the safety, efficacy, and PK of RYZ101 compared with investigator-selected standard of care (SoC) therapy in Part 2 in subjects with inoperable, advanced, well-differentiated, somatostatin receptor expressing (SSTR+) gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that have progressed following treatment with Lutetium 177-labelled somatostatin analogue (177Lu-SSA) therapy, such as 177Lu-DOTATATE or 177Lu-DOTATOC (177Lu-DOTATATE/TOC), or 177Lu-high affinity [HA]-DOTATATE.

Masking: None (Open Label)

Primary Purpose: Treatment

Official Title: Phase 1b/3 Global, Randomized, Controlled, Open-label Trial Comparing Treatment With RYZ101 to Standard of Care Therapy in Subjects With Inoperable, Advanced, SSTR+, Well-differentiated GEP-NETs That Have Progressed Following Prior 177Lu-SSA Therapy

Actual Study Start Date ⓘ : March 24, 2022

Estimated Primary Completion Date ⓘ : July 2025

Estimated Study Completion Date ⓘ : July 2028

Equipe multidisciplinar

- Oncologia
- Radiologia
- Radioterapia
- Medicina nuclear
- Patologia
- Genética médica
- Enfermagem
- Física médica

Conclusões

- Imagem molecular - características biológicas da doença.
- Tratamento direcionado com radionuclídeos emissores α ou β
- Minimização de toxicidade para tecidos normais
- Dados substanciais e crescentes apoiam a abordagem teranóstica
 - Aumento da sobrevida e melhora da qualidade de vida

Perspectivas

- Novos radiofármacos
- Combinação com outras terapias
- Fundamental ampliar acesso

Muito obrigado

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