PRISMAP
Medical Radionuclides

6th Consortium meeting

27-29 November 2023

IST-ID (Bobadela/Lisbon, Portugal)

Phase 1 clinical trials with medical radionuclides

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28 November 2023

Agenda

- Introduction.
- (Pre)Screening and FUP.
  - Clinical.
  - Pathological.
  - FUP during treatment.
  - Prescreening for treatment.
- Treatment.
  - Sequencial.
  - Avoiding toxicity.
  - “Patient journey”.
- Conclusions.

Introduction

- A radionuclide is a radioactive nuclide with an unstable nucleus that **dissipate** its excess **energy** by **spontaneously** emitting ionizing **radiation** (eg alpha, beta or gamma rays).
- It is also called **radioistope**, **radioactive isotope** or **radioactive nuclide**.
- In nuclear medicine, radionuclides are used for **diagnosis**, **treatment** and **research**.

What causes radioactivity?

- Radioactivity is caused by instability in the nucleus due to:
  - Imbalance in number of neutrons (N) and protons (Z)-**Natural Radionuclides.**
  - Excitation due to bombardment of particles-**Artificial Radionuclides.**

Properties

- Radionuclides are characterized by:
  - Activity.
  - Half-Life.
  - Energy.
  - Decay scheme.
  - Production method.

TABLE : PHYSICAL HALF-LIFE ($T_{P1/2}$) AND DECAY CONSTANT (λ) FOR RADIONUCLIDES USED IN NUCLEAR MEDICINE

Radionuclide	$T_{p1/2}$	λ
Fluorine 18 (^{18}F)	110 min	0.0063 m
Technetium 99m (^{99m}Tc)	6.02 hr	0.1151 hr^{-1}
Iodine 123 (^{123}I)	13.27 hr	0.0522 hr^{-1}
Samarium 153 (^{153}Sm)	1.93 d	0.3591 d^{-1}
Molybdenum 99 (^{99}Mo)	2.75 d	0.2522 d^{-1}
Indium 111 (^{111}In)	2.81 d	0.2466 d^{-1}
Thallium 201 (^{201}Tl)	3.04 d	0.2281 d^{-1}
Gallium 67 (^{67}Ga)	3.26 d	0.2126 d^{-1}
Xenon 133 (^{133}Xe)	5.24 d	0.1323 d^{-1}
Iodine 131 (^{131}I)	8.02 d	0.0864 d^{-1}
Phosphorus 32 (^{32}P)	14.26 d	0.0486 d^{-1}
Chromium 51 (^{51}Cr)	27.70 d	0.0250 d^{-1}
Strontium 89 (^{89}Sr)	50.53 d	0.0137 d^{-1}
Iodine 125 (^{125}I)	59.41 d	0.0117 d^{-1}
Cobalt 57 (^{57}Co)	271.79 d	0.0025 d^{-1}

Production Methods

METHOD OF RADIONUCLIDE PRODUCTION	ADVANTAGES	DISAVANTAGES
Cyclotron	•High specific activity. •Fewer radioistopes are produced. •It is easily accesible than nuclear reactor	•Expensive tu purchase and operate
Nuclear fission	•The fission process is a source of a number of widely used radioisotopes (90Sr, 99Mo, 131I and 133Xe) •High specific activity	•Large quantities of radioactive materials generated
Neutron activation	-	•It is difficult to separate chemically Low specific activity
Generator	•It is cheap •It is portable •High spcific activity •It is easy to operate	•It cannot be stored for future use

Commonly Used Radionuclides

- The primary radionuclide used for **diagnostic** nuclear medicine is **Technetium 99m**.
- The primary radionuclide used for **therapeutic** nuclear medicine is **Iodine-131**.
- The primary radionuclide used for Positron Emission Tomography (**PET**) is Fluorine-18-labelled De-oxyglucose (**FGD**).

Radiopharmaceuticals

- Pharmaceuticals are attached (labelled) to the radionuclide in order to send it to **desired target** within the body. The resultant mixture is called radiopharmaceuticals.
- Compose of a radionuclide **bond** to an organic molecule.
- Radiopharmaceuticals are designed to **concentrate** on a particular organ/tissue.
- Mimic a **natural physiologic process**.
- Evaluate **function** rather than anatomy.

Desirable properties of radiopharmaceuticals

- **Localize** largely and quickly in a target organ.
- **Eliminate**d from the body with effective $T_{1/2}$ similar to duration of examination.
  - Effective $T_{1/2}$ should be long enough to complete the study, but short enough to minimize patien dose.
- Have **low toxicity**.
- Form **stable** product in vivo and in vitro.
- **Minimal electron contamination**.
- Contain **no** chemical or radionuclide **contaminants**.
- Be **readily** and **cheap** available.

Advantages of radiopharmaceuticals

- More precise than surgery or RT. Avoiding healthy tissue injury.
- They can reach tumors that are difficult to reach with other treatment methods.
- May be less expensive than other treatment methods.

Disadvantages of radiopharmaceuticals

- Adverse events:
  - Fatigue.
  - Nausea/vomiting.
  - Myelosupression.
- Difficult administration.

Types of therapies

- **Targeted radiopharmaceuticals** – These radiopharmaceuticals are designed to bind to specific molecules on cancer cells. This allows the radiopharmaceutical to concentrate on cancer cells, reducing damage to healthy tissues.
- **Controlled-release radiopharmaceuticals** – These radiopharmaceuticals are designed to release radiation in a controlled manner over a period of time. This can help increase the effectiveness of the treatment and reduce side effects.
- **Combination radiopharmaceuticals** – These radiopharmaceuticals combine radiation with other treatments, such as chemotherapy or immunotherapy. This can help improve treatment results.

Radionuclides for therapy

- ^{131}I treatment of thyroid cancer.
- ^{131}I treatment in hyperthyroidism.
- Radioimmunotherapy with ^{90}Y ibritumomab tiuxetan (Zevalin) and ^{131}I tositumomamab (Bexxar) therapy of low-grade non-Hodgkin´s lymphoma.
- They can be administered in capsule or liquid solution form.

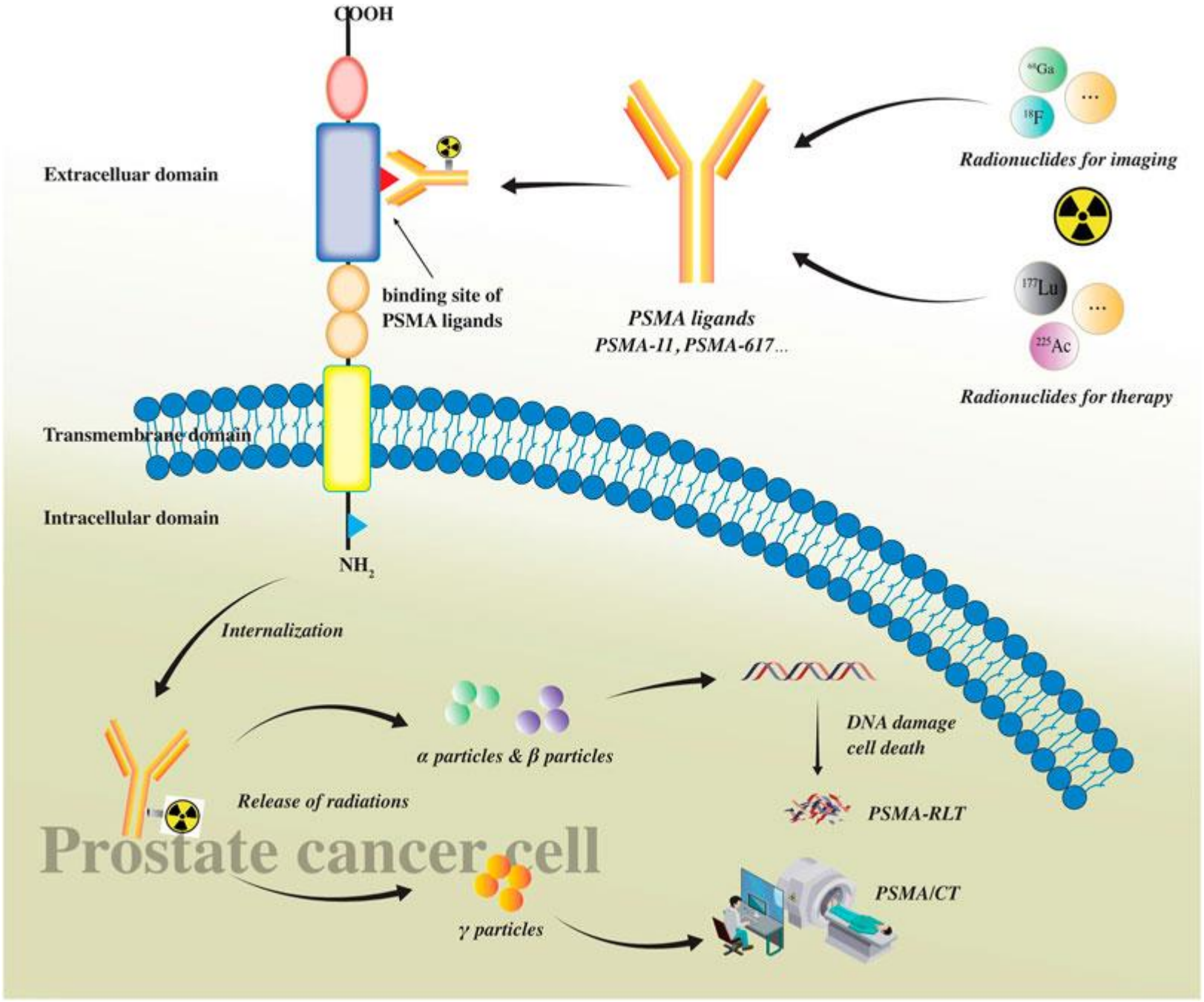
Current applications approved for treatment

Radiopharmaceutical	Active Ingredient	Cancer Type	Approval Date
Xofigo®	Radium-223 dichloride	Metastatic castration-resistant prostate cancer	2013
Hicon®	Sodium iodide I-131	Thyroid cancer	1971
Azedra®	Lobenguane iodine-131	Pheochromocytomas and paragangliomas	2012
Quadramet®	I-131 metaiodobenzylguanidine	Neuroendocrine tumors	2008
Zevalin®	Yttrium Y-90 ibritumomab tiuxetan	Non-Hodgkin's lymphoma	2002
Lutathera®	Lutetium Lu-177 dotatate	Neuroendocrine tumors	2018
Pluvicto™	Lutetium Lu-177 vipivotide tetraxetan	Prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer	2021
SkyScrin®	Gallium Ga-68 dotatoc	Neuroendocrine tumors	2018
Myloview™	Iodine-131 I-bensamidin	Myeloma	2021

Receptor	Radionuclide	Study drug	Conditions	Accrual goal	Status/date of completion	Phase	NCT
SSTR	^{90}Y	^{90}Y-DOTA-tyr3-Octreotide	Neuroendocrine Tumor, Carcinoid Tumor, Neuroblastoma, Medulloblastoma	39	5/27/20[a]	2	NCT03273712
	^{67}Cu	^{67}Cu-SARTATE	Neuroblastoma, Relapsed Neuroblastoma and Refractory Neuroblastoma	34	Recruiting	2	NCT04023331
	^{68}Ga	^{68}Ga-DOTATATE-	Hepatocellular Carcinoma	12	2/3/22[b]	2	NCT03648073
PSMA	^{177}Lu	^{177}Lu-PSMA-617	Progressive Metastatic Castration Resistant Prostate cancer	200	12/31/21[c]	2	NCT03392428
	^{177}Lu	^{177}Lu-DOTA-TLX591	Biochemically Recurrent Oligometastatic, Prostate Specific Membrane Antigen-Expressing Prostate Cancer	50	Recruiting	2	NCT05146973
	^{67}Cu	^{67}Cu-SAR-bisPSMA	Metastatic Castrate Resistant Prostate Cancer (mCRPC)	44	Recruiting	2	NCT04868604
	^{177}Lu	^{177}Lu-PSMA-617	Prostatic Neoplasms	20	Active/Not Recruiting	2	NCT04430192
	^{177}Lu	^{177}Lu-ITG-PSMA-1	Soft Tissue Sarcoma	20	Recruiting	1	NCT05420727
FAP	^{177}Lu	^{177}Lu-DOTA-FAPI	Locally Advanced or Metastatic Cancer	30	Recruiting	1	NCT04849247
	^{177}Lu	^{177}Lu-FAP-2286	Advanced Solid Tumors	170	Recruiting	1 + 2	NCT04939610
FGFR3	^{225}Ac	^{225}Ac-FPI-1966, ^{111}In-FPI-1967	Advanced Solid Tumor, Head and Neck Squamous Cell Carcinoma, Bladder Carcinoma, Susceptible FGFR3 Genetic Alterations, FGFR3, FGFR3 Protein Overexpression, Ovarian Cancer, Colorectal Cancer, Breast Cancer, Liver Cancer, Lung Cancer, Gastric Cancer	155	Recruiting	1 + 2	NCT05363605
CCK2 Receptor—Gastrin analog	^{177}Lu	^{177}Lu-PP-F11N	Thyroid Cancer, Medullary; Neuroendocrine Tumor of the Lung Grade 1 and 2; Neuroendocrine Tumor of the Thymus Grade 1 and 2; Neuroendocrine Tumor GEP Grade 1-3	24	Recruiting	1	NCT02088645
CD46	^{89}Zr	^{89}Zr-DFO-YS5	mCRPC	24	Recruiting	1	NCT05245006

Healy A, Ho E, Kuo P and Zukotynski K (2023)

PRESCREENING & FUP.


COOH
Extracelluar domain
binding site of
PSMA ligands
PSMA ligands
PSMA-11, PSMA-617...
Radionuclides for imaging
Radionuclides for therapy
Transmembrane domain
Intracellular domain
NH2
Internalization
α particles & β particles
Release of radiations
DNA damage
cell death
PSMA-RLT
Prostate cancer cell
γ particles
PSMA/CT

Correlation Between Quantitative PSMA PET Parameters and Clinical Risk Factors in Non-Metastatic Primary Prostate Cancer Patients

Sebastian Zschaeck[1,2†], Stephanie Bela Andela[1†], Holger Amthauer[3], Christian Furth[3], Julian M. Rogasch[2,3], Marcus Beck[1], Frank Hofheinz[4] and Kai Huang[3]*

- [68Ga] Ga-PSMA-11 PET/CT imaging
- Serum (PSA) values.
- clinical T stage.
- Gleason scores

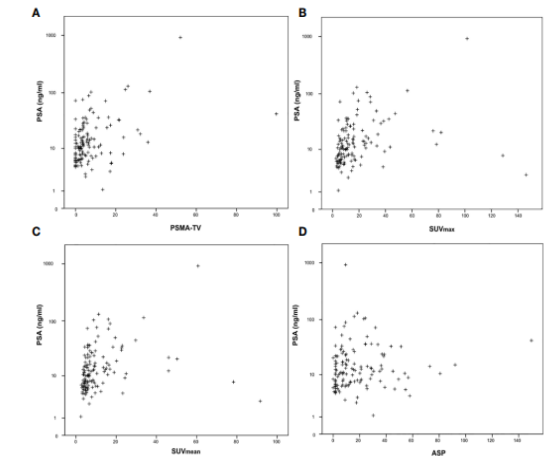


FIGURE 1 | Correlation between serum prostate-specific antigen (PSA) values and quantitative PSMA-PET parameters. **(A)** PSMA-derived tumor volume (PSMA-TV), **(B)** Maximum standardized uptake value (SUVmax), **(C)** Mean standardized uptake value (SUVmean) and **(D)** Tumor asphericity (ASP). PSA values are plotted on a logarithmic scale.

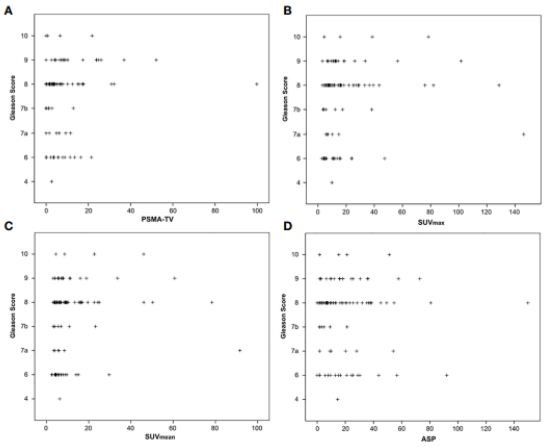


FIGURE 2 | Correlation between Gleason scores obtained by biopsy before imaging and quantitative PSMA-PET parameters. **(A)** PSMA-derived tumor volume (PSMA-TV), **(B)** Maximum standardized uptake value (SUVmax), **(C)** Mean standardized uptake value (SUVmean) and **(D)** Tumor asphericity (ASP).

Histology and PSMA Expression on Immunohistochemistry in High-Risk Prostate Cancer Patients: Comparison with ^{68}Ga-PSMA PET/CT Features in Primary Staging

Luigia Vetrone [1,*,†], Riccardo Mei [1,†], Lorenzo Bianchi [2], Francesca Giunchi [3,*], Andrea Farolfi [4], Paolo Castellucci [4], Matteo Droghetti [2], Massimiliano Presutti [2], Alessio Degiovanni [3], Riccardo Schiavina [2], Eugenio Brunocilla [2], Antonietta D'Errico [3] and Stefano Fanti [4]

- 138 pts high-risk Prostate Cancer.
- ^{68}Ga PSMA-PET/CT.
- Radical prostatectomy.

Table 5. Correlations among PET-parameters and histopathology features.

	pT- SUVmax	PSMA-TV	PSMA-TL
HYSTOTYPE	/	Higher values are related to cribriform (*p*-value 0.04)	/
VISUAL SCORE	Higher values displayed VS 3+ (*p*-value 0.03)	/	Higher values displayed VS 3+ (*p*-value 0.025)
VISUAL PATTERN	/	/	Membranous (*p*-value 0.009)
VISUAL GROWTH	/	/	/
LVI	/	Predictive value (*p*-value 0.002)	Predictive value (*p*-value 0.01)
PNI	/	/	/

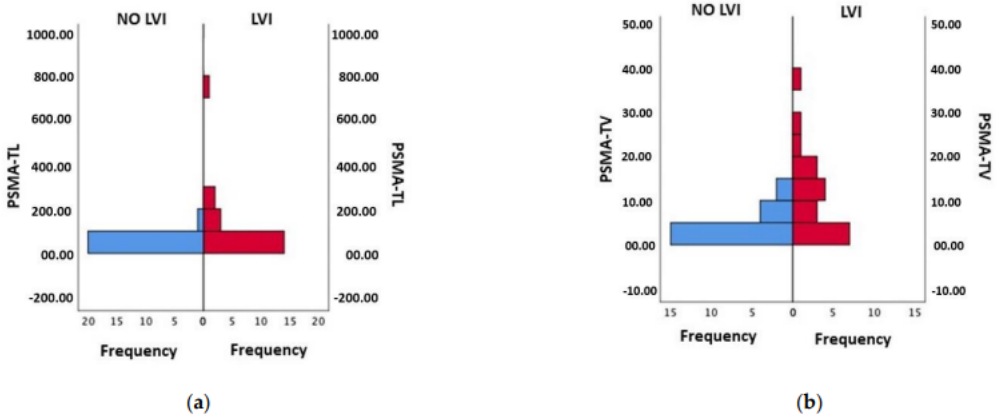
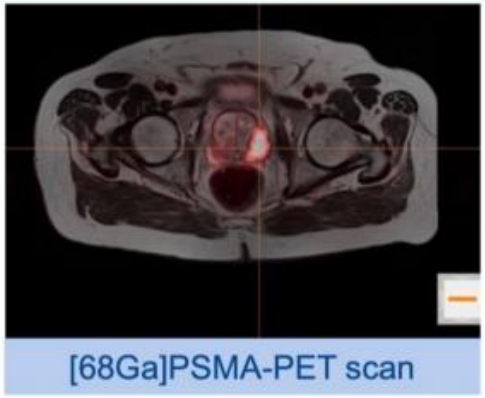


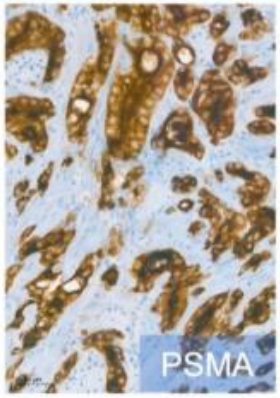
Figure 3. (**a**) Mann–Whitney Test for PSMA-TL and LVI (*p*-value 0.01); (**b**) Mann–Whitney Test for PSM-TV and LVI (*p*-value 0.002).

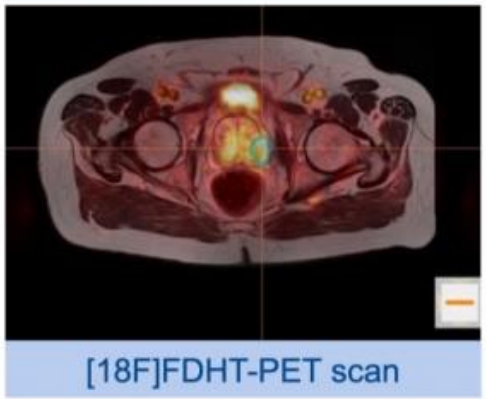
Consecutive PSMA and AR PET imaging shows positive correlation to AR and PSMA protein expression in primary hormone naïve prostate cancer.

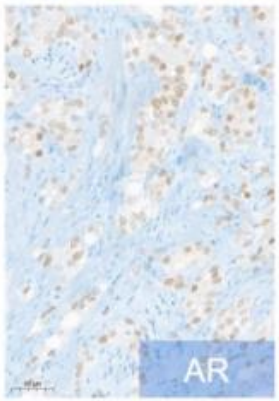
Valentin al Jalali[1,2], Gabriel Wasinger[3], Sazan Rasul[4], Bernhard Grubmüller[5], Beatrix Wulkersdorfer[1, 2], Theresa Balber[1,4], Markus Mitterhauser[1, 4, 6], Judit Simon[1, 7], Marcus Hacker[4], Shahrokh Shariat[8], Gerda Egger[1, 3, 9], Markus Zeitlinger[1, 2]#

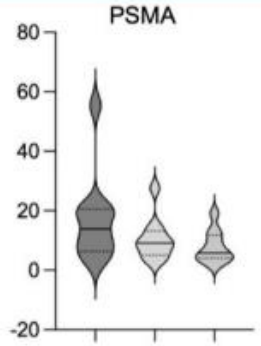
[68Ga]PSMA and [18F]FDHT PET imaging shows positive correlation to androgen receptor (AR) and PSMA protein expression in primary hormone naïve prostate cancer.

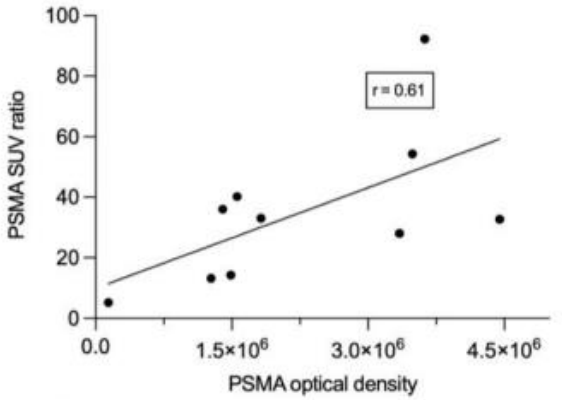


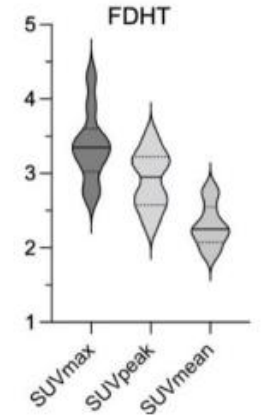


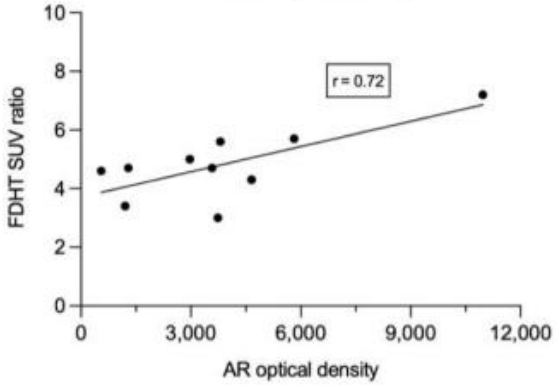












TREATMENT

PSMA-Alpha Targeted Radionuclide Therapy with or without Prior PSMA-Beta Targeted Radionuclide Therapy

Patient Characteristics	Prior Beta-TRT	No Prior Beta-TRT
Number	21	64
Median PSA (ng/mL)	171.25 (range 4.79 – 2209.87)	35 (2.43 – 9614)
Median Age at Treatment	70 (range 60 – 88)	71.5 (51 – 91)
Halabi Risk Category		
Low	0 (0%)	10 (16%)
Intermediate	6 (29%)	22 (34%)
High	15 (71%)	32 (50%)
Therapy		
^{225}Ac-J591 Single-Dose[1]	14 (67%)	17 (27%)
^{225}Ac-J591 Fractionated[2]	4 (19%)	20 (31%)
^{225}Ac-J591 + ^{177}Lu-PSMA-I&T[3]	1 (5%)	17 (27%)
^{225}Ac-J591 + Pembro[4]	2 (9%)	10 (16%)
Prior Taxane Chemotherapy	13 (62%)	38 (59%)
>1 Prior ARPI	14 (67%)	36 (56%)
Median # EBRT	1 (range 0-3)	1 (0 – 6)
Prior Radium-223	3 (14%)	12 (19%)
Lymph Node Metastasis	13 (62%)	36 (56%)
Liver Metastasis	2 (9%)	8 (13%)
Lung Metastasis	3 (14%)	7 (11%)
Bone Metastasis	19 (90%)	54 (84%)
^{68}Ga-PSMA-11 SUVmax	58.8 (range 9.6-129)	34.7 (3 – 105.7)
Median Administered ^{225}Ac Activity (KBq/kg)	80 (range 13.3 – 130)	80 (35 – 130)

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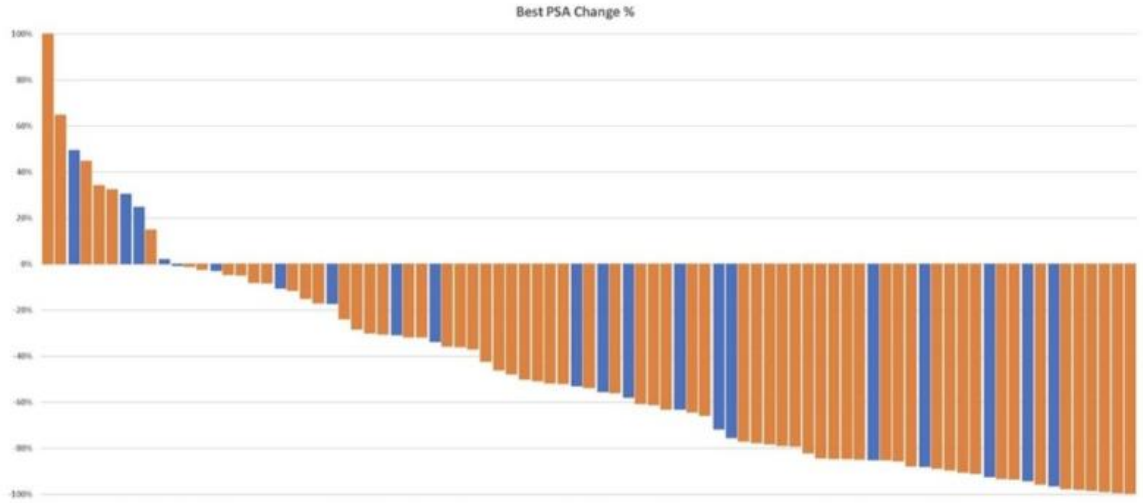
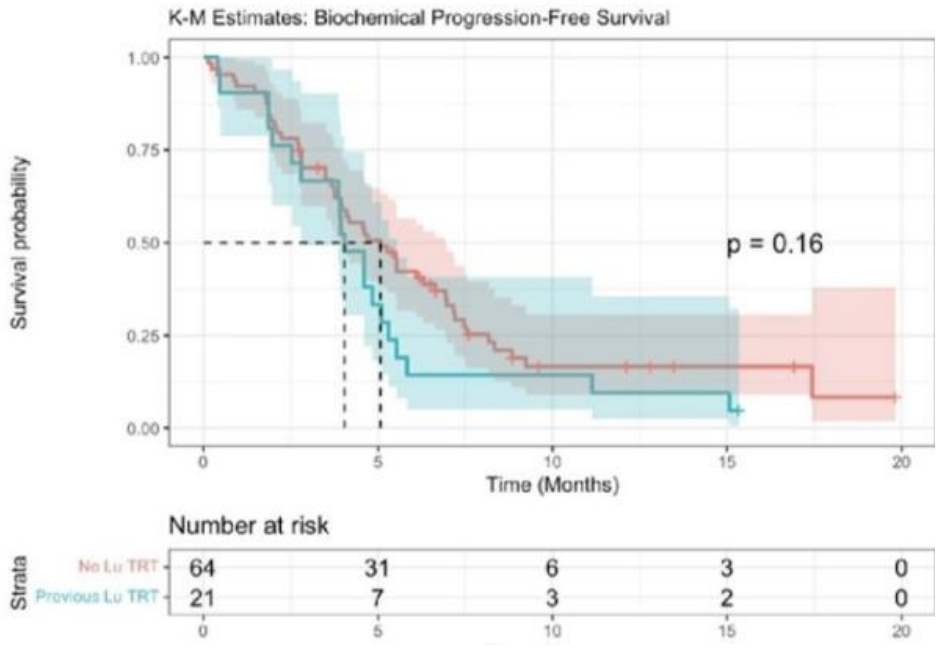
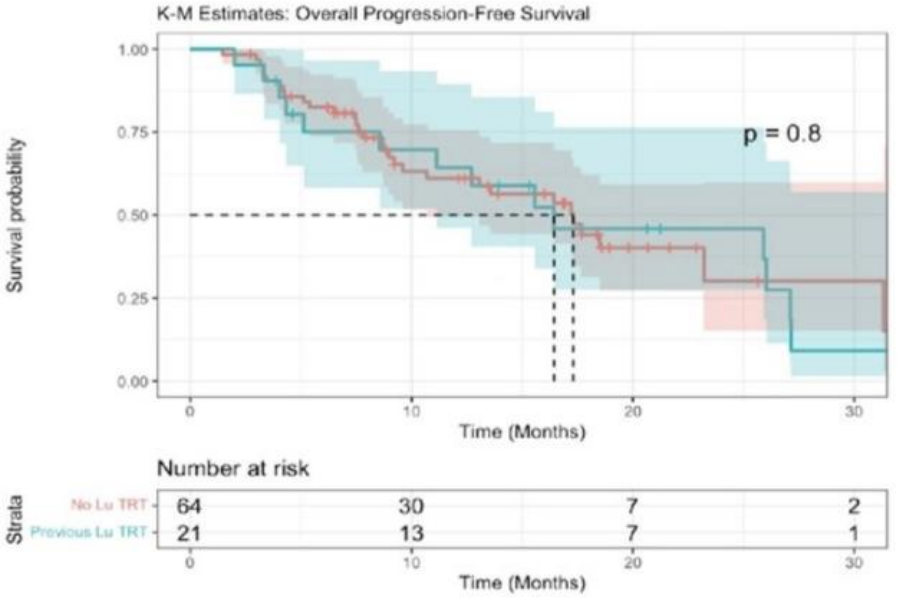
Adverse Event	Prior Beta-TRT (N=21)	No Prior Beta-TRT (N=64)
Grade 1-2 Neutrophil	6 (29%)	24 (37%)
Grade 3-4 Neutrophil	2 (9%)	6 (9%)
Grade 1-2 Platelet	12 (57%)	36 (56%)
Grade 3-4 Platelet	3 (14%)	13 (20%)
Grade 1-2 Anemia	8 (38%)	17 (27%)
Grade 3-4 Anemia	2 (9%)	9 (14%)
Pain	10 (48%)	37 (58%)
Xerostomia	10 (48%)	39 (61%)
Fatigue	17 (81%)	47 (73%)
Nausea	14 (67%)	37 (58%)
Cr Elevation	1 (5%)	5 (8%)
AST Elevation	7 (33%)	29 (45%)



Biochemical Progression-Free Survival



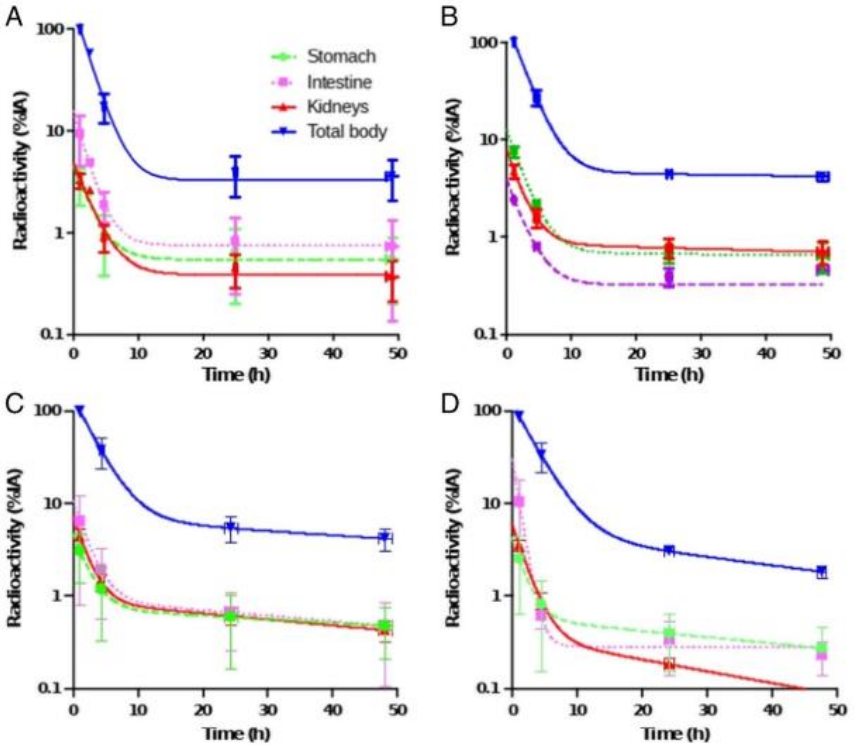
Overall Survival



No significant difference PSA50 (52 vs 58%), PFS (4.03 vs 5.07 mo), or OS (16.4 vs 17.3 mo)

[^{111}In]In-CP04 as a novel cholecystokinin-2 receptor ligand with theranostic potential in patients with progressive or metastatic medullary thyroid cancer: final results of a GRAN-T-MTC Phase I clinical trial

Luka Lezaic[1,2] · Paola Anna Erba[3] · Clemens Decristoforo[4] · Katja Zaletel[1,2] · Renata Mikolajczak[5] · Helmut Maecke[6] · Theodosia Maina[7] · Mark Konijnenberg[8] · Petra Kolenc[1,9] · Malgorzata Trofimiuk-Müldner[10] · Elwira Przybylik-Mazurek[10] · Irene Virgolini[4] · Marion de Jong[8] · Alide C Fröberg[8] · Christine Rangger[4] · Gianpaolo Di Santo[4] · Konrad Skorkiewicz[11] · Piotr Garnuszek[5] · Bogdan Solnica[12] · Berthold A. Nock[7] · Danuta Fedak[12] · Paulina Gaweda[12] · Alicja Hubalewska-Dydejczyk[10]



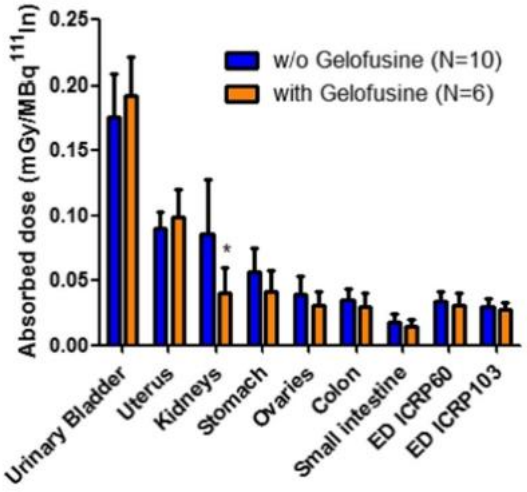
Phase I multicenter clinical trial – GRAN-T-MTC

16 eligible patients with progressive or metastatic MTC (positive [^{18}F]FDG PET-CT/CT/MRI or elevated calcitonin and/or positive calcitonin doubling time)

Phase 1A:
4 patients
Two peptid amounts:
10 and 50 µg CP04

NO severe adverse events

Phase 1B:
50 µg CP04
Arm 1: with Gelofusine administration
Arm 2: without Gelofusine administration




THANK YOU!