FAP-based radiotheranostics for the treatment of diverse adenocarcinomas and sarcomas (including combinations with immune- and chemotherapeutics)

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President Academy, International Centers for Precision Oncology (ICPO)

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WORLD ASSOCIATION OF RADIOPHARMACEUTICAL AND MOLECULAR THERAPY
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www.curanosticum.de

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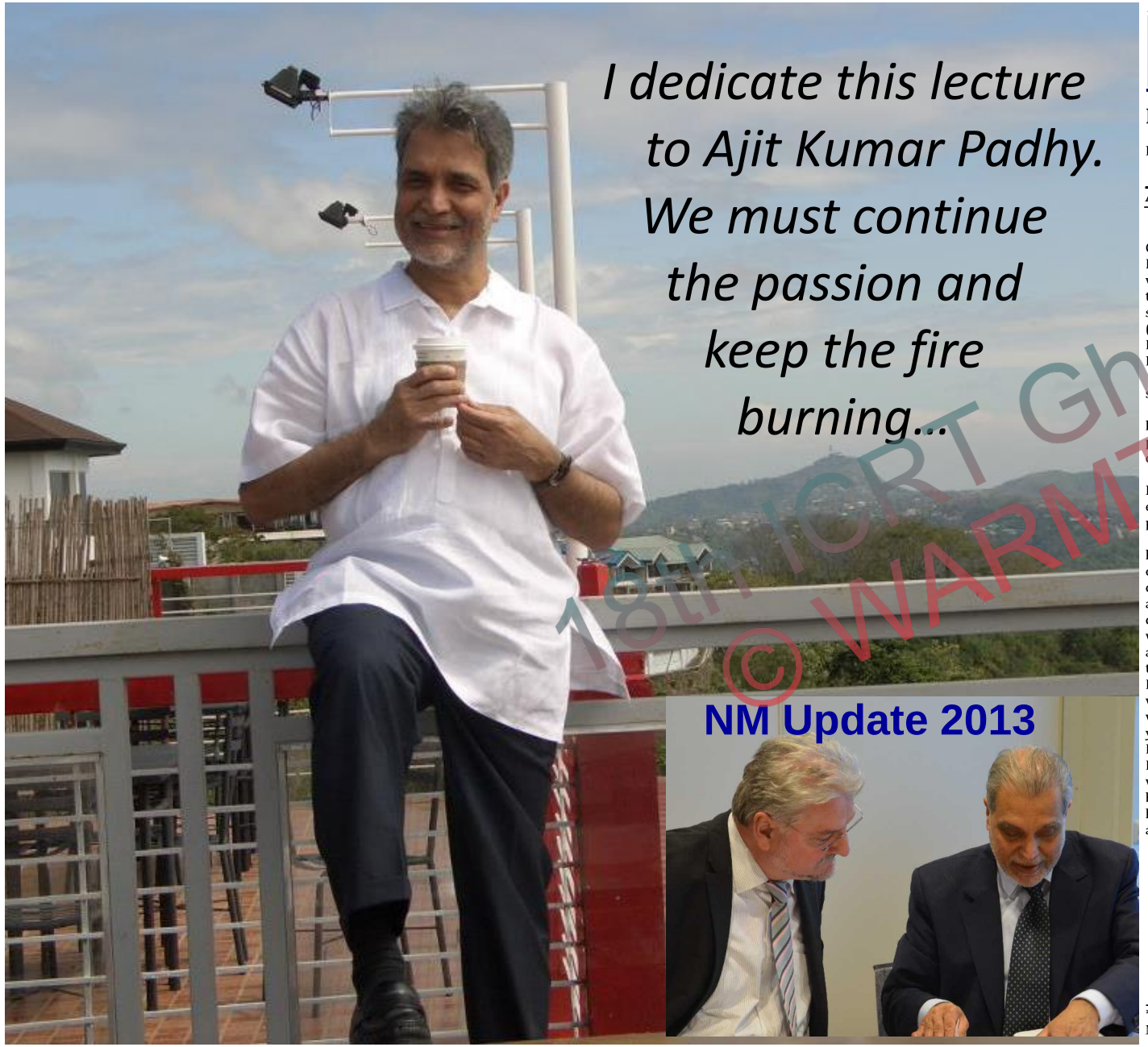
Potential conflicts of interest

Type of affiliation or financial support	Sponsor
President, ICPO Academy , Chairman Scientific Board Member, ICPO Board of Trustees	No payments
Consultant	Curanosticum Wiesbaden-Frankfurt
Scientific Advisory Board (SAB) Consulting	ITM, **3B Pharma (3BP),** Telix, Sinotau, Jiangsu Huayi Technology (JHT), Full Life Technologies, Portland Holding, z Alpha
Research Grants Research Contracts	ITM, Novartis, Ipsen, Shaanxi, 3BP, TELIX, benfovir, oxy5, Starget Pharma
Clinical Study/Trial	ITM, Advanced Accelerator Applications, Novartis, Ipsen Pharma
Stockholder of a Healthcare Company/ Investment Interest	Telix, Clovis Oncology, ITM, Endocyte, benfovir, Eckert & Ziegler (EZAG), PINAX, BAMF Health
Founder/Cofounder:	RPO Group/NucleoGenesis, 1717 LSV, PentixaPharm, PositronPrecision, Molecular Targeted Radiopharma-ceuticals (MTR), RadioVaxx, RadioDoxx
Scientific Meetings Support	ITM, MONROL, EZAG, 3BP, Novartis *and many others* see www.twc-2022.org



Asia Oceania Journal of Nuclear Medicine & Biology
http://aojnmb.mums.ac.ir
AOJNMB

In Memoriam-Professor Ajit K.Padhy

Emerita Andres Barrenechea

ARTICLE INFO

Article type: Obituary

Dr. Ajit Kumar Padhy MD, FAMS was a Senior Consultant, Department of Nuclear Medicine & PET at Singapore General Hospital, Singapore when he passed away on 22nd August 2013. Prior to this, he was Head of the Nuclear Medicine section International Atomic Energy Agency (IAEA), in Vienna for seven years. He was also Head of Nuclear Medicine at the All India Institute of Nuclear medicine, New Delhi, India.

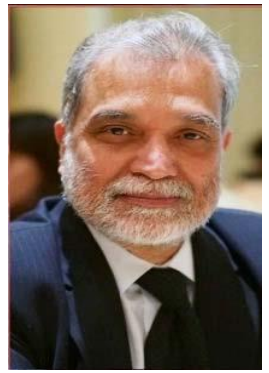
His untimely demise left a wife and two loving sons, accomplished in their own rights.

In the realm of Nuclear Medicine, the specialty he loved so much, he left a worldwide league of physicians and colleagues orphaned. His passion of the specialty will remain unsurpassed.

His selfless devotion to uplift the practice of Nuclear Medicine in developing countries, encourage young doctors to do research and his peers to excel in this field was limitless.

Born in Orissa, where he enjoyed his childhood, he will remain a treasure that belongs to the entire world. He loved life, and was even described by his classmates to be "enterprising and flamboyant". He loved music, movies and dancing. He also loves to cook and his cooking was delicious. To us his colleagues, he was stylish and paid attention to small details when it comes to arranging meetings /conferences (being in the IAEA for 7 years and doing this around the world). He is so confident, kind and generous. He was honest and critical especially if it will be for your betterment and without intention to hurt.

In 2009, he co-founded the World Association of Radiopharmaceutical and Molecular Therapy where he was President till 2012 when he became the Executive Director. WARMTH now has more than 400 members around the globe and his loss is so strongly felt. He is also Editor in



Chief of the "World Journal of Nuclear Medicine" at the time of his death. This was another "baby" of his, spending sleepless nights beating the deadline. He was also an active member of editorial board of the "Asia Oceania Journal of Nuclear Medicine & biology". He had hundreds of published papers and chapter of books. His advocacy for therapy for thyroid cancer, thyrotoxicosis and liver cancer are seen in most of his works.

To all of us whose lives he has touched, we deeply mourn his passing away.

His challenge to make a better world through therapy especially in oncology must be a reminder to those he left behind.

We must continue the passion and keep the fire burning for his works, a legacy he left. He will always be an inspiration for us. May he attain peace, and happiness in the life beyond.

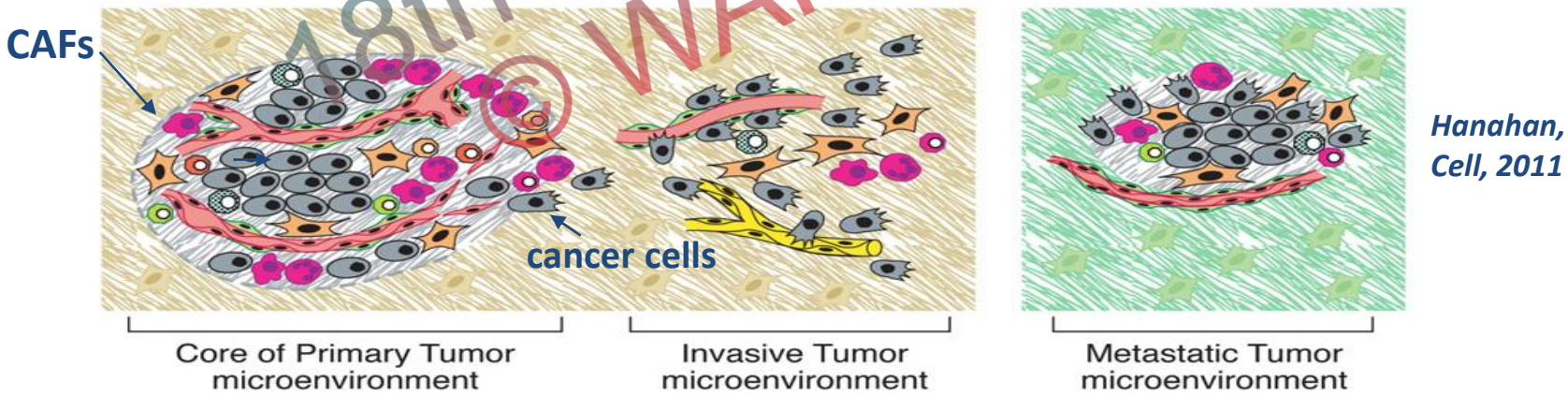
For a minute's silence, everyone, please stand up

*Corresponding author: Emerita Andres Barrenechea MD, Department of Nuclear Medicine, Veterans Memorial Medical Centre, North Avenue, Diliman, Quezon City-1100, Philippines departmant.

Tumor Microenvironment

Fibroblast activation protein (FAP) is a selective marker of cancer-associated fibroblasts (CAFs) which are expressed in 90% of all malignant tumors.

- CAFs are highly prevalent in the tumor microenvironment (TME) of many cancer entities.
- CAFs persist in the TME throughout all malignant stages of tumorigenesis.
- CAFs express FAP which represents a pan-tumor target.
- FAP is not expressed on normal fibroblasts, thus FAP expression in normal tissues is very low.



Hanahan, Cell, 2011

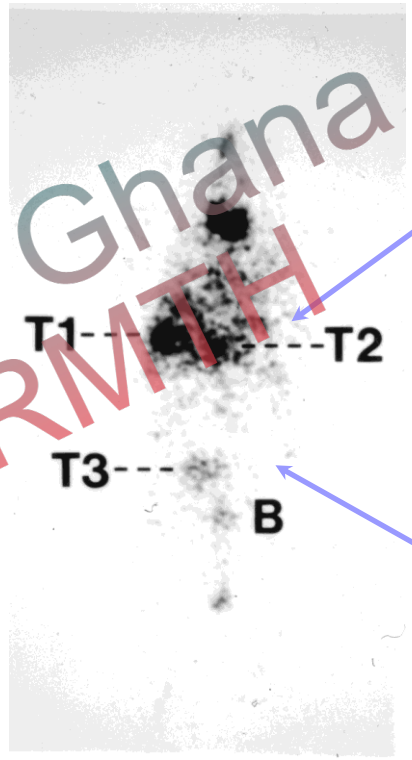
TARGET was first described by P. Garin-Chesa, Wolfgang J. Rettig and Lloyd J. Old (MSKCC) 1990

Garin-Chesa P, Old LJ, Rettig WJ. Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. PNAS. 1990;87:7235–7239;

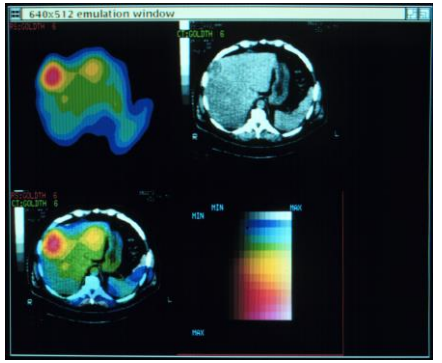
First-in-human Trial – ^{131}I-F19

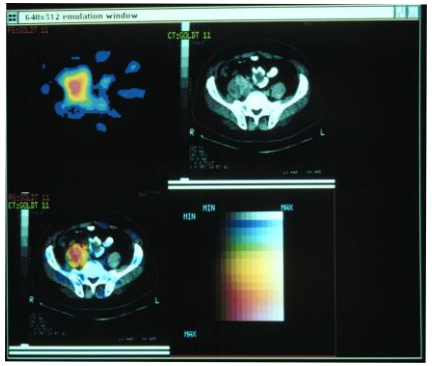
J Clin Oncol 12: 1193-1203, 1994 *Courtesy Andrew Scott*

- 17 pts with metastatic colorectal cancer, scheduled for surgery
- gradual clearance of ^{131}I-F19 from blood pool with time, no normal tissue uptake
- optimal localisation of ^{131}I-F19 at 4-5 days post injection
- occult disease detected in 2 pts
- biopsy samples from surgery (Day 7)
- tumour uptake reached 16.5 x 10^{-3} %ID/gm
  - tumour / liver ratios $\leq$ 21:1
  - tumour / serum ratios $\leq$ 9:1



Anterior gamma camera image 4 days post infusion ^{131}I-F19





SPECT and CT images

P. Garin-Chesa, Wolfgang J. Rettig, and Lloyd J. Old (MSKCC) published a paper in 1990 titled "Fibroblast activation protein: a cell surface dipeptidyl peptidase and matrix metalloprotease expressed by stromal fibroblasts in tissue remodeling and cancer"

FAP & Cancer

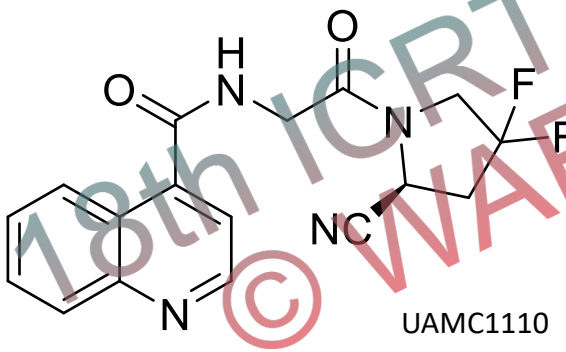
- Increased FAP expression on CAFs in the tumor-associated stroma of >30 different malignant tumors and sometimes also on the cell surface of certain cancer types (e.g., PDAC cells, gastric cancer cells, ovarian cancer, breast cancer, sarcomas…).
- FAP expression in normal tissue is usually very low or undetectable.
- Rule of thumb: FAP expression *often* associated with worse clinical outcome and tumor progression.
- However, there are controversial findings in certain cancer types and the distinct mode of action on tumor proliferation, migration and invasion of FAP is not totally clear yet - immunosuppression?
- Also, tumor suppressive effects of FAP were described.

Fitzgerald AA, Weiner LM. The role of fibroblast activation protein in health and malignancy. Cancer Metastasis Rev. 2020;39(3): 783–803.

FAP-inhibitor Structure-Activity Relationship

Affinity for FAP
vs **Selectivity**
among other DPPIV-members and PREP

IC_{50} (FAP)	=	3.2 nM
IC_{50} (PREP)	=	1.8 µM
IC_{50} (DPP4)	≥	100 µM
IC_{50} (DPP8/9)	>	12.5 µM
IC_{50} (DPP2)	>	100 µM



UAMC1110

Journal of Medicinal Chemistry
Article
pubs.acs.org/jmc

Extended Structure–Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP)

Koen Jansen,[†] Leen Heirbaut,[†] Robert Verkerk,[∥] Jonathan D. Cheng,[‡] Jurgen Joossens,[†] Paul Cos,[§] Louis Maes,[§] Anne-Marie Lambeir,[∥] Ingrid De Meester,[∥] Koen Augustyns,[†] and Pieter Van der Veken*[,†]

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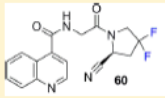
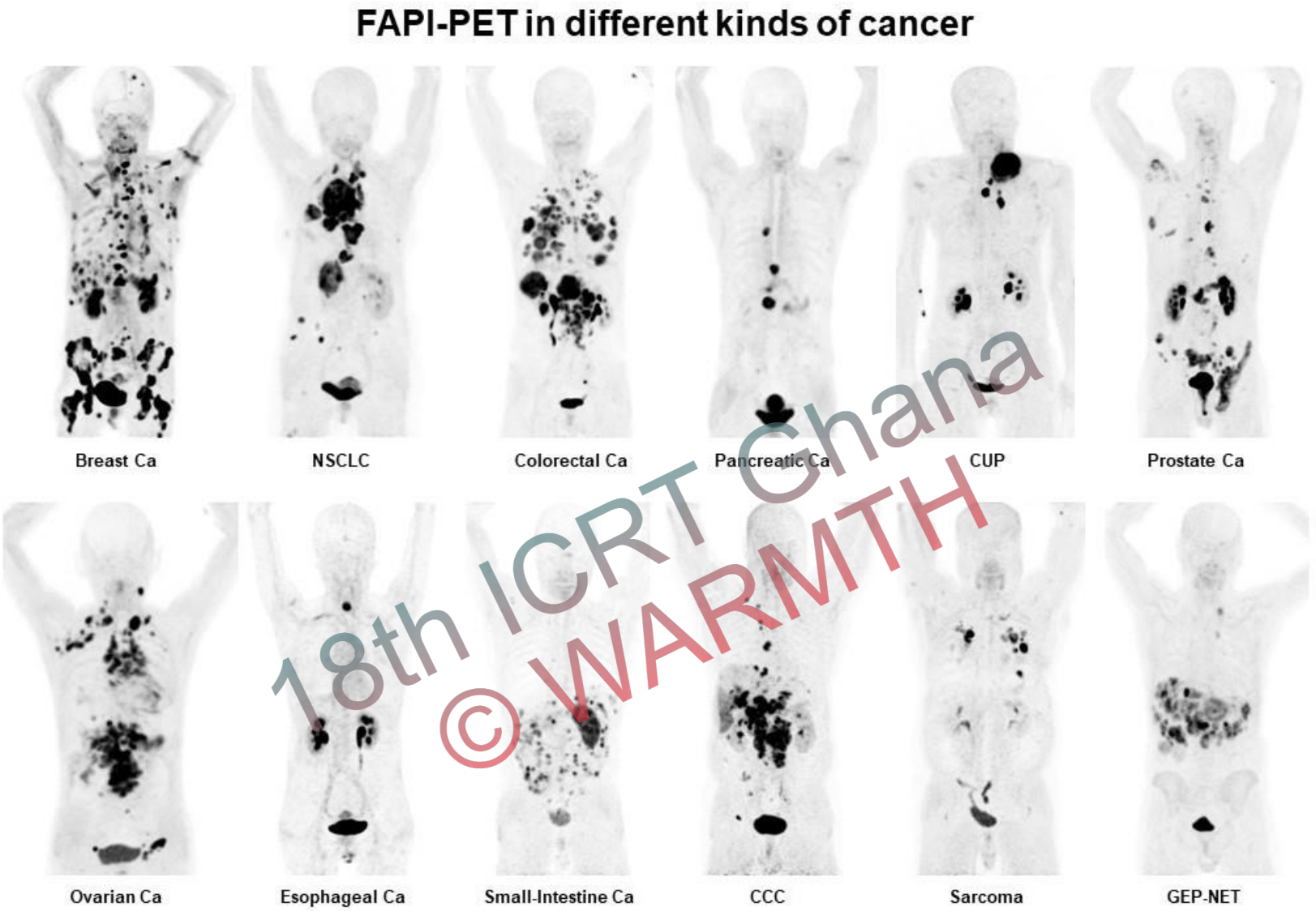
Supporting Information

ABSTRACT: Fibroblast activation protein (FAP) is a serine protease related to dipeptidyl peptidase IV (DPPIV). It has been convincingly linked to multiple disease states involving remodeling of the extracellular matrix. FAP inhibition is investigated as a therapeutic option for several of these diseases, with most attention so far devoted to oncology applications. We previously discovered the *N*-4-quinolinoyl-Gly-(2*S*)-cyanoPro scaffold as a possible entry to highly potent and selective FAP inhibitors. In the present study, we explore in detail the structure–activity relationship around this core scaffold. We report extensively optimized compounds that display low nanomolar inhibitory potency and high selectivity against the related dipeptidyl peptidases (DPPs) DPPIV, DPP9, DPPII, and prolyl oligopeptidase (PREP). The log *D* values, plasma stabilities, and microsomal stabilities of selected compounds were found to be highly satisfactory. Pharmacokinetic evaluation in mice of selected inhibitors demonstrated high oral bioavailability, plasma half-life, and the potential to selectively and completely inhibit FAP in vivo.



IC_{50}(FAP)= 3.2 nM
IC_{50}(PREP)= 1.8 µM
-Oral bioavailability in rats: 51%
-Circulating half-life: 3.2 hours
-Potent, long-lasting *in vivo* FAP-inhibition

Koen Jansen...**Pieter van der Veken** (University of Antwerp)
Extended Structure Activity Relationship and Pharmacokinetic Investigation of
(4-Quinolinoyl)glycy1-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP)
Journal of Medicinal Chemistry March ***2014***



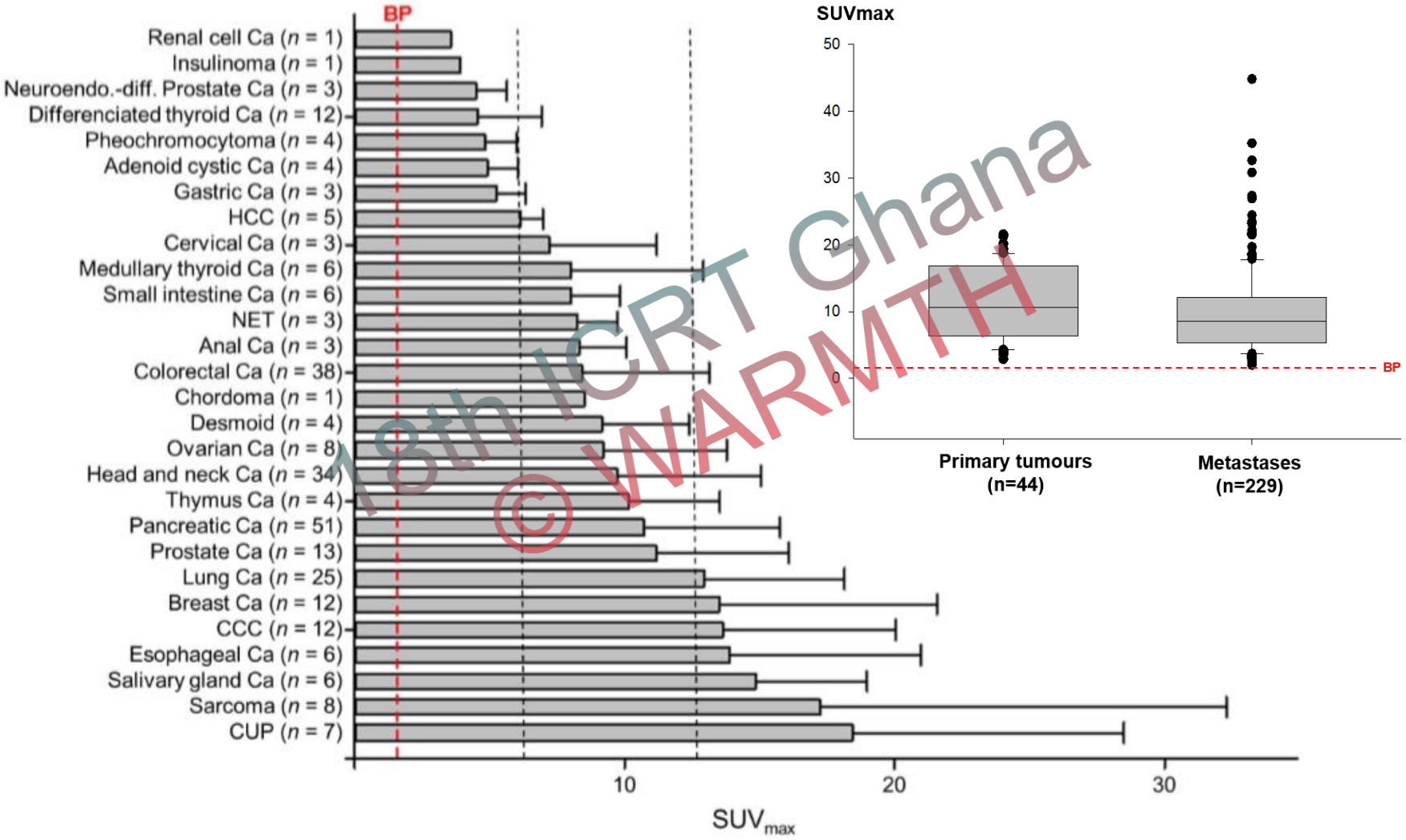
SNMMI 2019 Image of the Year:

^{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.*

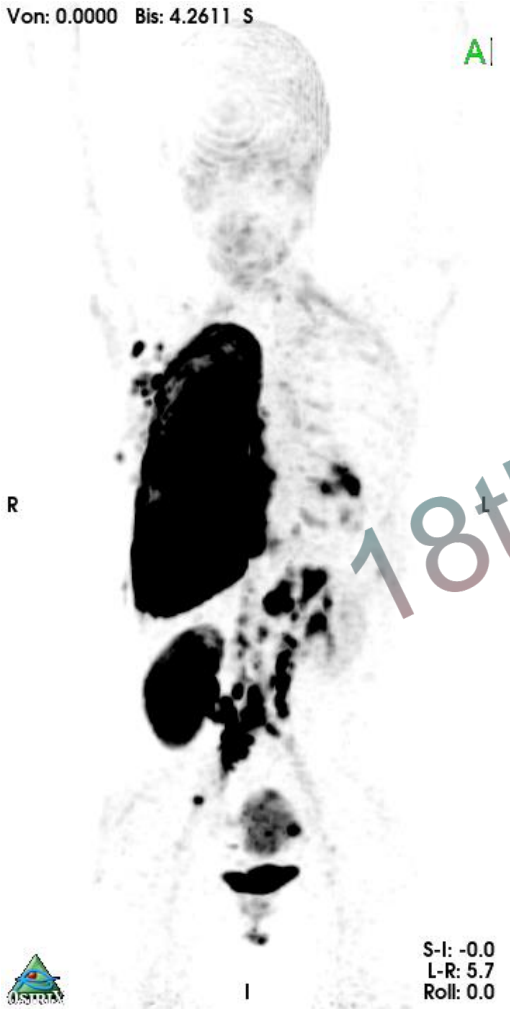
Cancer Associated Fibroblast (CAF)

FAPI-SUV in 28 different cancer entities

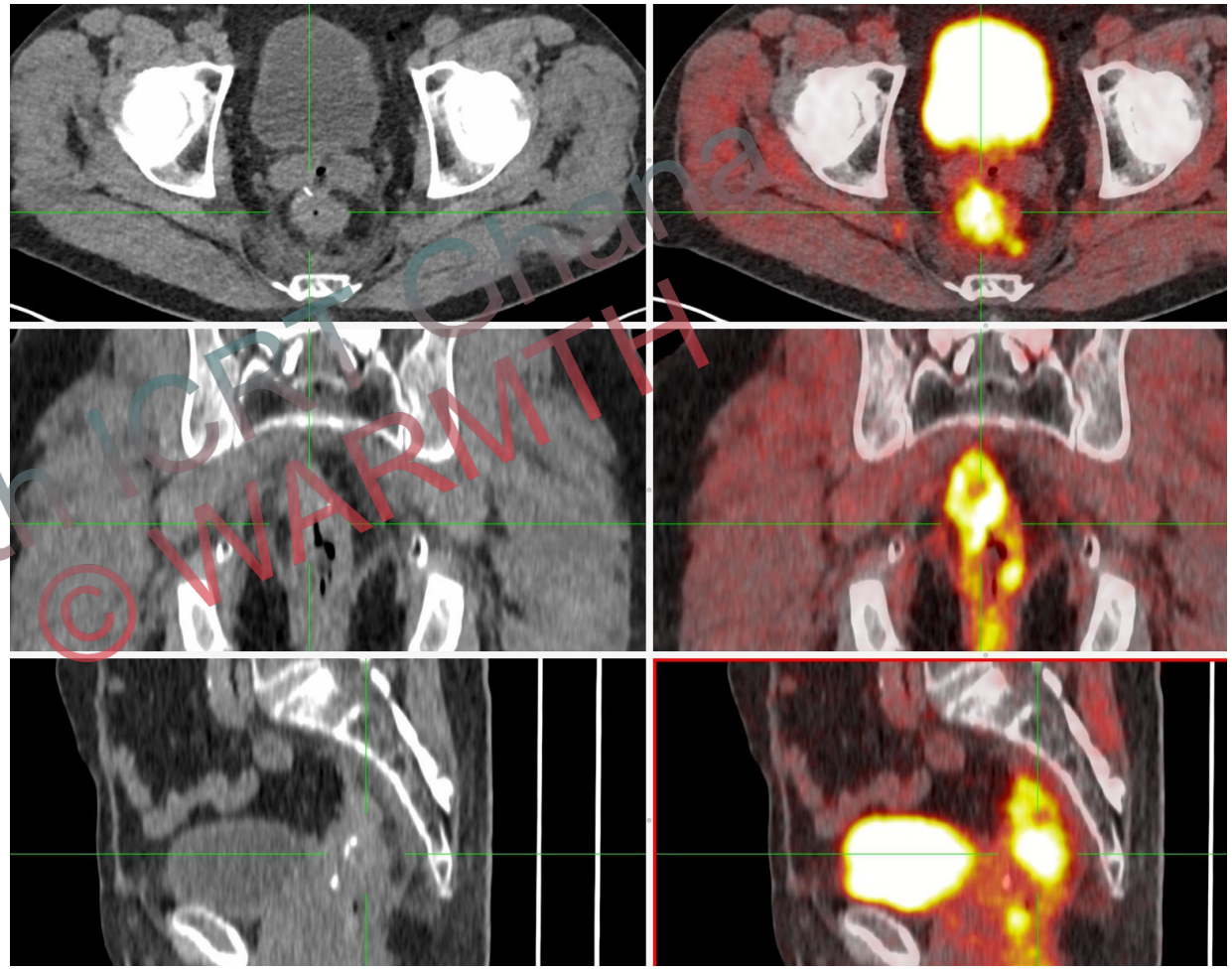


Kratochwil C, …Giesel FL, JNM 2019

Ga-68 **DATA** FAPi PET/CT (ligand provided by Frank Rösch, Mainz)



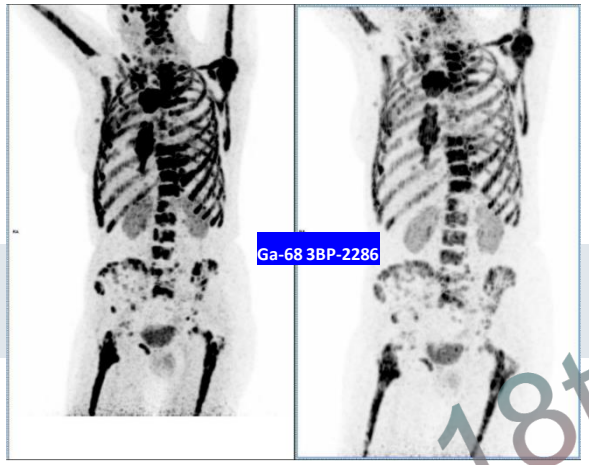
Breast cancer metastases



Rectal cancer

FAP-2286 Peptide: Excellent tumor accumulation, specificity and tumor retention in multiple cancer types after Peptide Targeted Radiotherapy (PTRT)

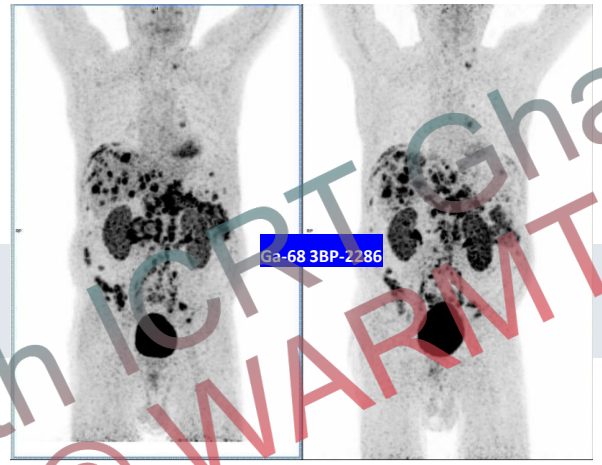
Breast Cancer



October 4, 2019 December 11, 2019

- **node, hepatic, lung, and extensive bone metastases (PR)**

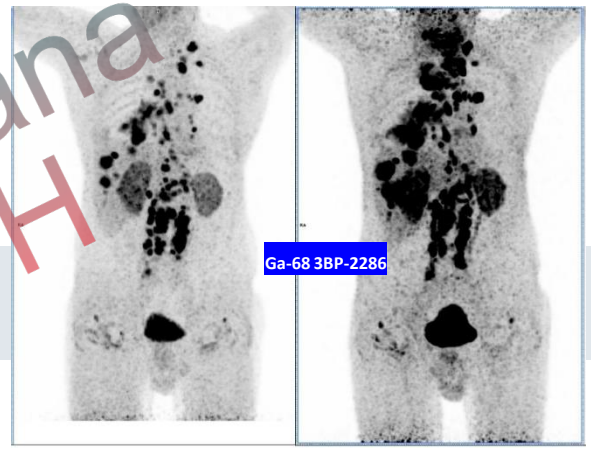
Pancreatic Cancer



October 4, 2019 December 11, 2019

- **Primary tumor, peritoneal, bilateral liver, and lymph node metastases (SD)**

Colorectal Cancer

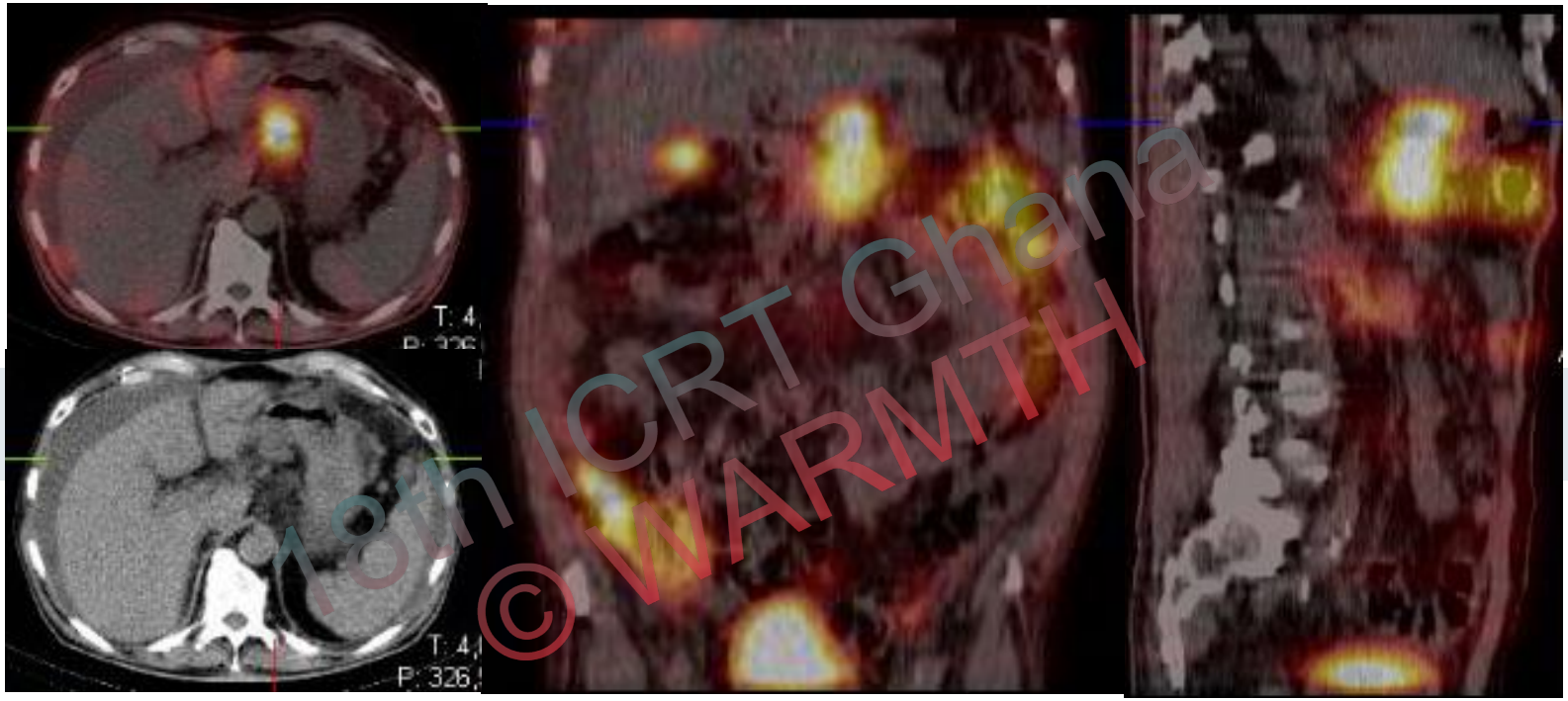


October 23, 2019 December 11, 2019

- **lung metastases (PD)**

ICPO Foundation Symposium December 2019, Zentralklinik Bad Berka , Germany

Worldwide first Peptide Targeted Radiotherapy (PTRT) using Lutetium-177 FAP-2286 peptide



Transversal SPCET/CT – upper row and CT scan – lower row showing uptake in the primary tumor

Coronal SPECT/CT demonstrating uptake in the primary and in liver and peritoneal metastases

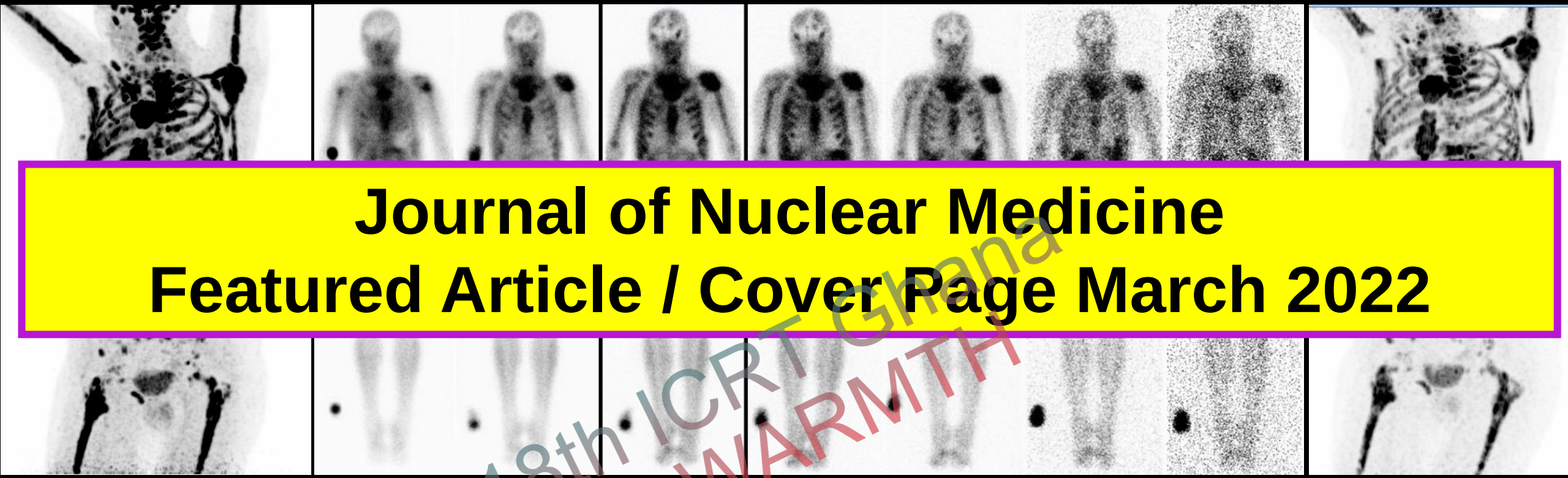
Sagittal SPECT/CT Intense uptake of the radiolabeled peptide in the pancreatic cancer

Lu-177 FAP SPET/CT 44 h after administering the treatment activity:

specific and persistent uptake in the pancreatic adenocarcinoma

and in liver and peritoneal metastases

Baum RP. ICPO Foundation Symposium December 2019, Zentralklinik Bad Berka , Germany



Journal of Nuclear Medicine
Featured Article / Cover Page March 2022

^{68}Ga-FAP-2286 PET/CT before therapy

^{68}Ga-FAP-2286 PET/CT after therapy

Serial ^{177}Lu-FAP-2286 whole-body scans at different time points after injection: uptake and retention of the radiopeptide (up to 10 days) in metastatic lesions

64-year-old female with ductal breast cancer (ER / PR 90 % positive, HER-2 negative), extensive bone and bone marrow metastases as well as lymph node and pulmonary involvement. Pat. had undergone surgery, radiotherapy (EBRT) to bone metastases and pain palliation with radiolabeled biphosphonates and strictly refused chemotherapy. PTRT using 2.4 GBq ^{177}Lu-FAP-2286 was performed leading to dramatic improvement of diffuse bone pain.

Post-therapy ^{68}Ga-FAP-2286 PET/CT demonstrated a mixed response – regression of bone and bone marrow lesions, but also progression of liver metastases.

J Nucl Med 2022; 63:415–423
DOI: 10.2967/jnumed.120.259192

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

Richard P. Baum*[1,2], Christiane Schuchardt[1], Aviral Singh[1], Maythinee Chantadisai[1,3], Franz C. Robiller[1], Jingjing Zhang[1,4], Dirk Mueller[1], Alexander Eismant[1], Frankis Almaguel[1,5], Dirk Zboralski[6], Frank Osterkamp[6], Aileen Hoehne[6], Ulrich Reineke[6], Christiane Smerling[6], and Harshad R. Kulkarni*[1]

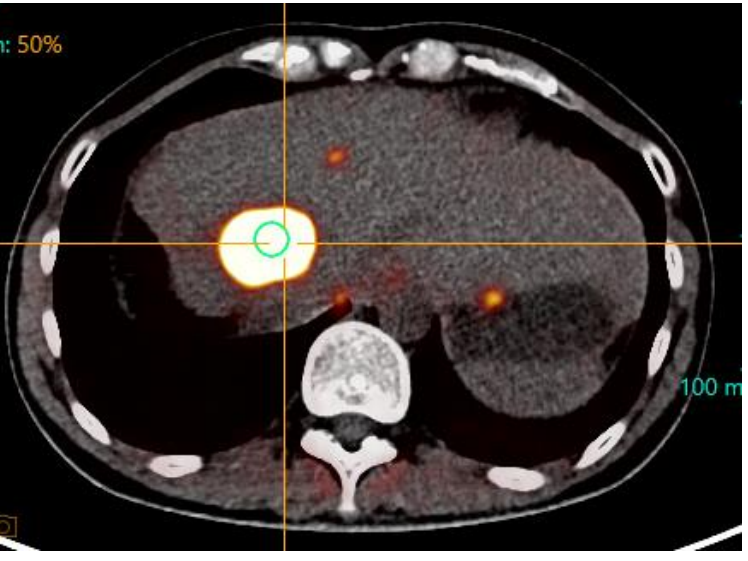
[1]Theranostics Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik Bad Berka, Bad Berka, Germany; [2]Curanosticum Wiesbaden–Frankfurt, Center for Advanced Radiomolecular Precision Oncology, Wiesbaden, Germany; [3]Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [4]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [5]Loma Linda University, Loma Linda, California; and [6]3B Pharmaceuticals GmbH, Berlin, Germany

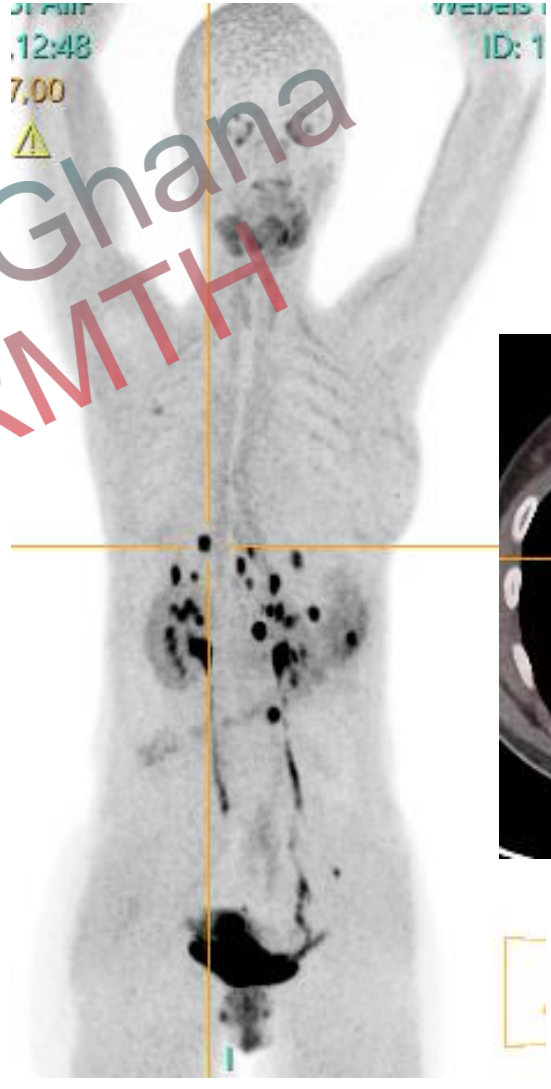
PTRT using 3BP-3940

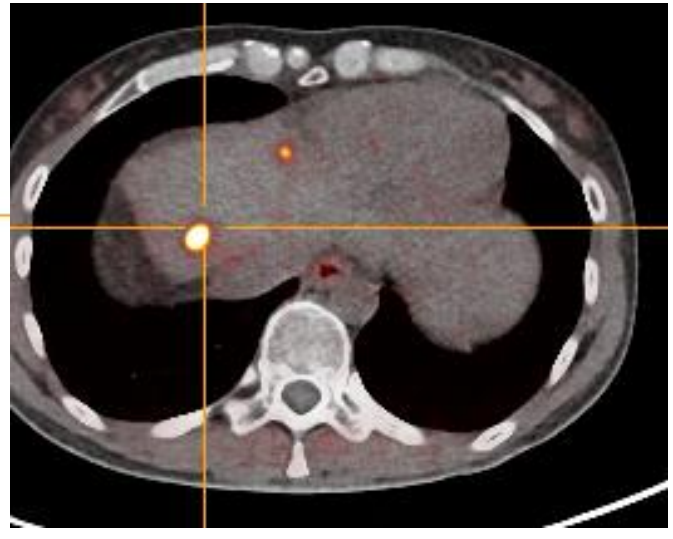
- **PTRT was performed since March 2021 in 45 patients with advanced adenocarcinomas** after prior confirmation of significant tumor uptake (SUV tumor-to-background ratio > 3) on **^{68}Ga-3BP-3940.**
- **Biodistribution was analyzed by post-therapy SPET/CT (skull to mid thigh) and whole-body images.**
- **Clinical parameters, laboratory findings (CTCAE v5.0) and tumor markers were monitored.**
- **^{177}Lu-, ^{90}Y-, and ^{225}Ac-FAP-3BP-3940, respectively, were administered intravenously over one minute.**
- **No renal protection was performed.**
- **The injected activity was chosen individually based on the patients' clinical conditions, hematologic and renal function as well as uptake in the tumor lesions and total tumor burden (personalized approach).**
- **Additional cycles were administered when patients consented and if condition allowed for further treatment.**
- **Response to therapy was determined by molecular (^{68}Ga-FAP-3BP-3940 PET/CT and ^{177}Lu-FAP SPET/CT) and morphological imaging (ceCT / MRI) and by monitoring tumor-associated antigens (CEA, CA 19-9, CA 125, CA 15-3).**

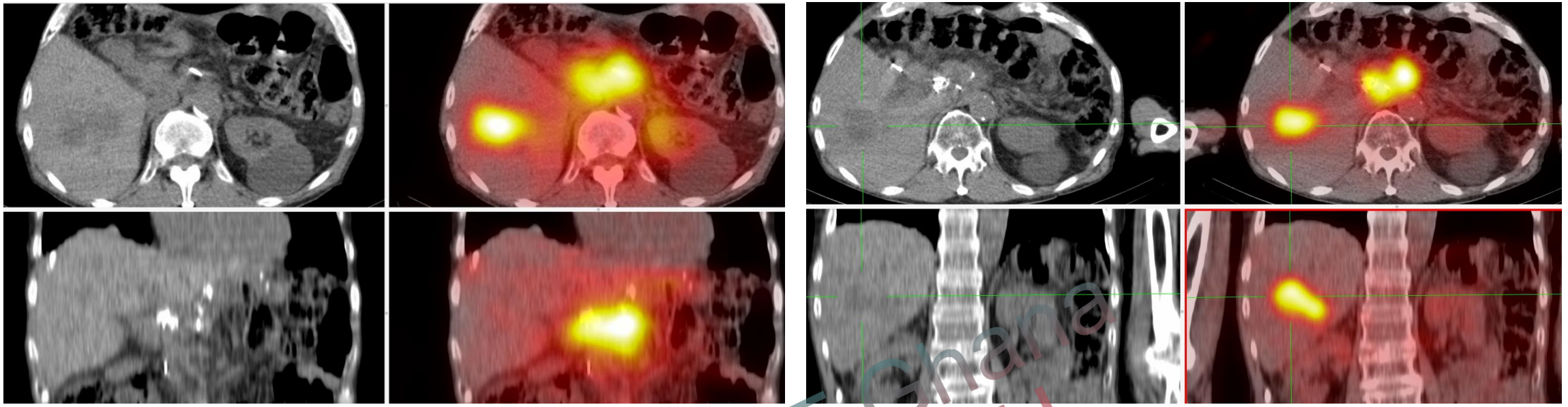
Metastatic Clear Cell Sarcoma of Small Bowel

Baseline and 8 Months Follow-Up (Ga-68 3BP-3940 FAP)

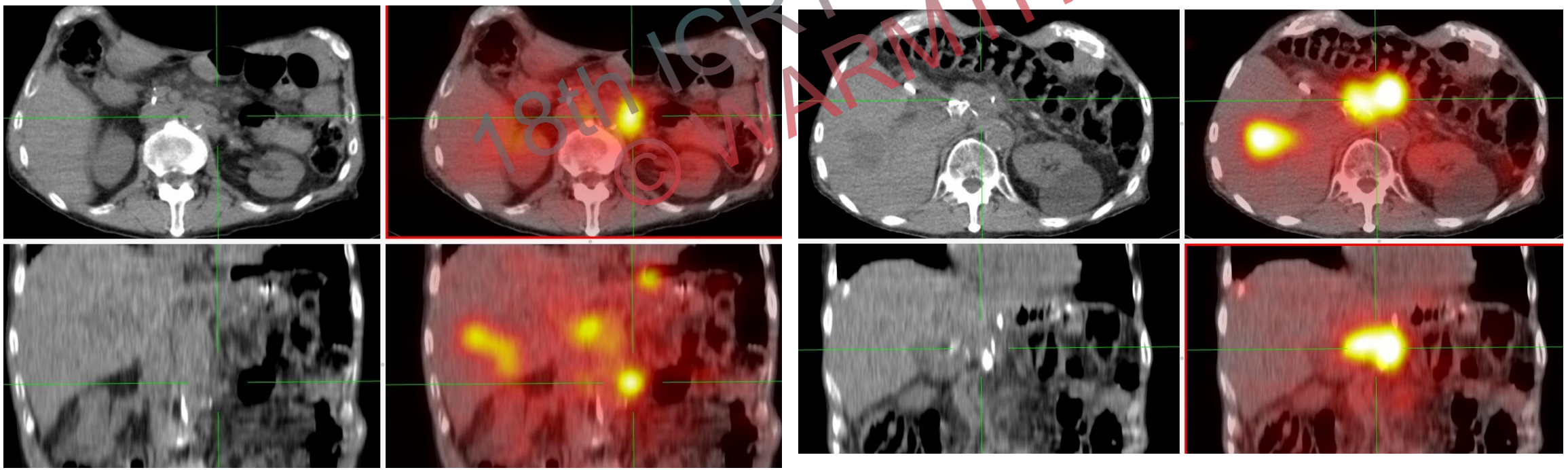








Lu-177 + Ac-225 FAP-3BP SPET/CT: 2 hrs - L upper corner, 48 hrs - R upper, and 144 hrs – R lower corner

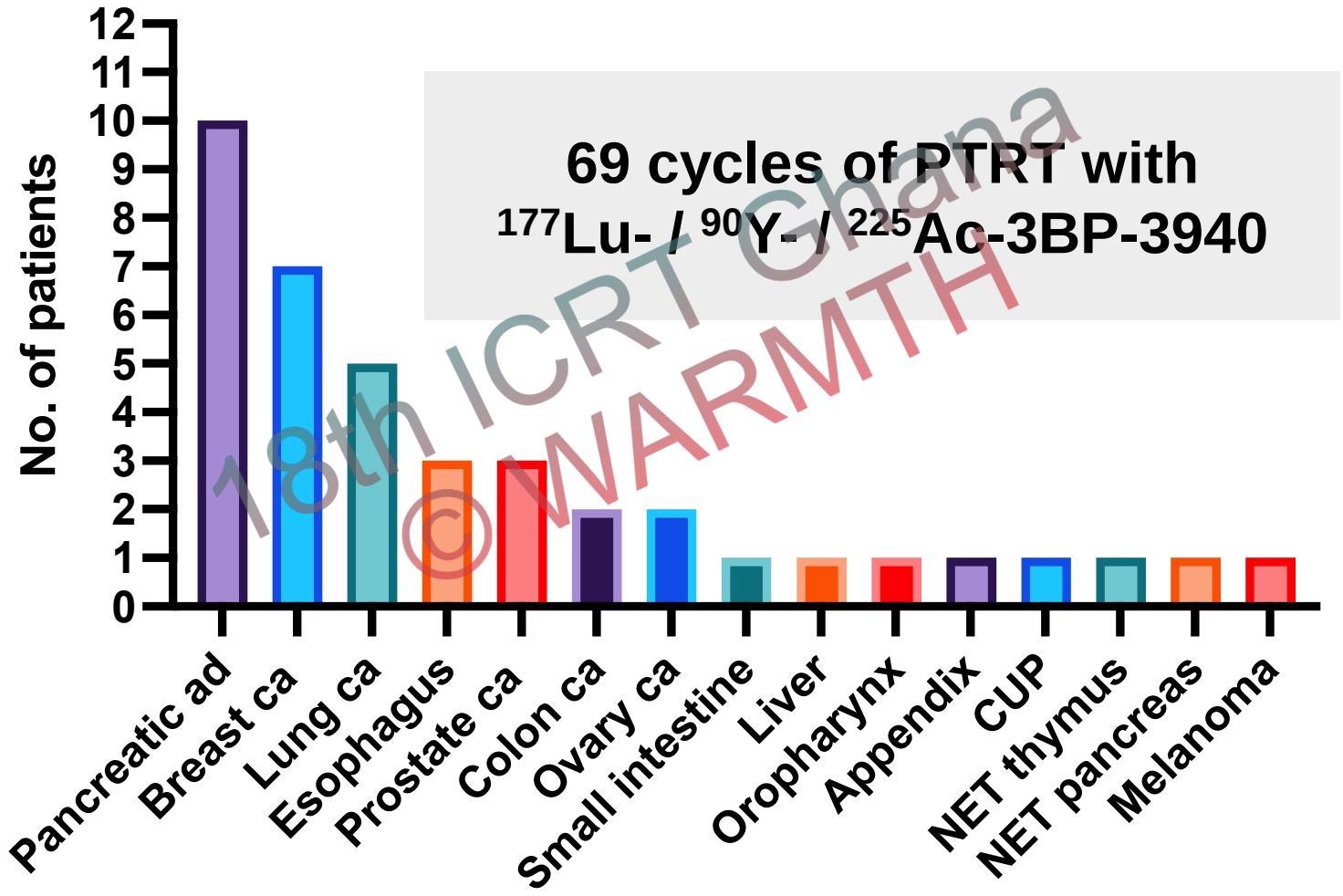


Pancreatic adenocarcinoma, liver & LN metastases

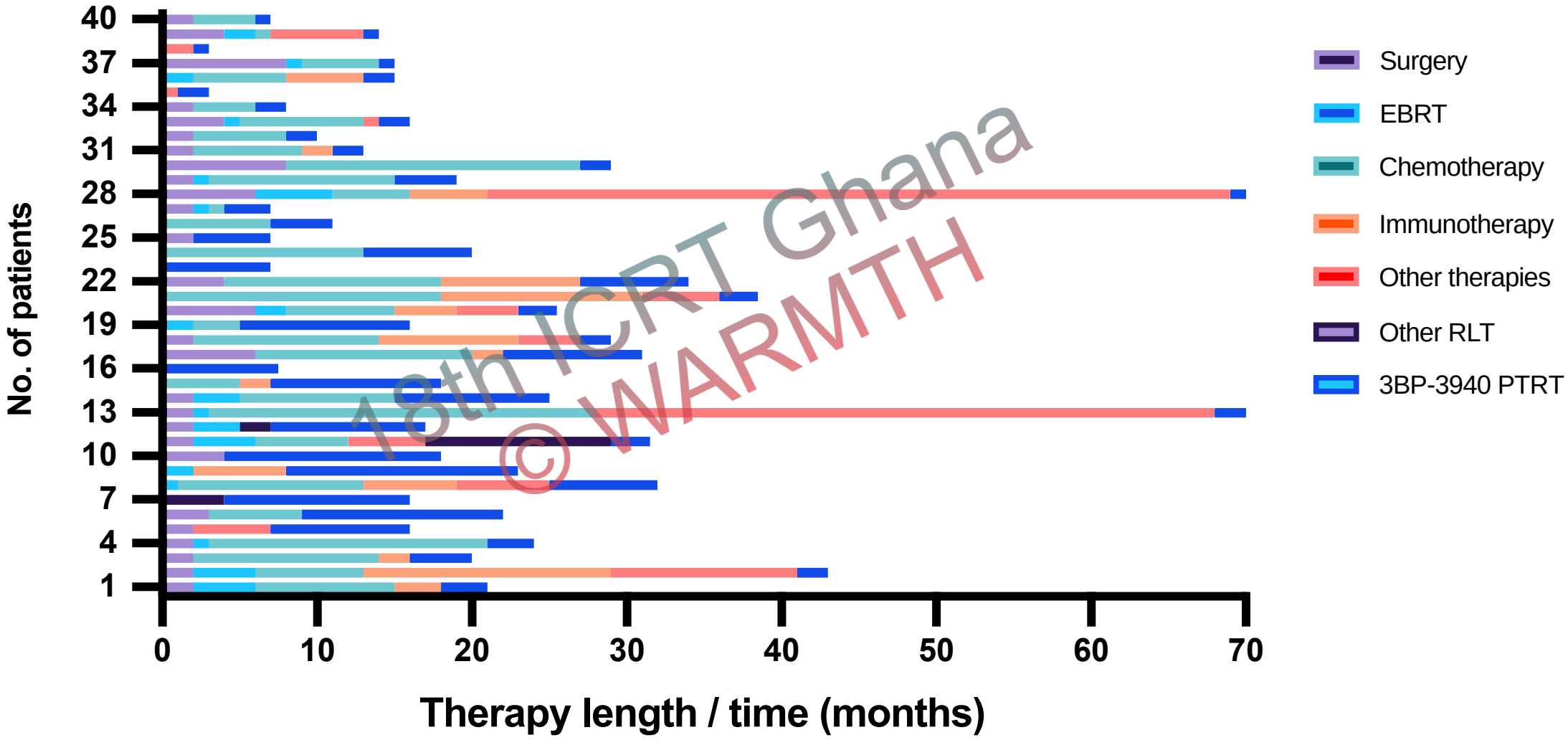
R.P. Baum and colleagues, Curanosticum Wiesbaden-Frankfurt
17-May-2021

PRIMARY TUMOR	NUMBER OF PATIENTS	MEAN AGE
Pancreatic tumor	12	59.5
Breast cancer	7	51.5
Lung (NSCLC) Adenocarcinoma	4	61.3
Esophagus	4	63.7
Prostate cancer	3	68.6
Ovarian carcinoma	2	62
Oropharynx (SCC)	1	56
Small intestine sarcoma	1	37
Appendix	1	58
Urothelial carcinoma	1	72
Hepatocellular carcinoma	1	72
Colon carcinoma	1	70
Signet cell carcinoma (CUP)	1	78
Uveal melanoma	1	57
Atypical lung carcinoid	1	69
Thymus neoplasia	1	54
Uveal Melanoma	1	57

PTRT using 3BP-3940 – Primary Tumors (n = 40)



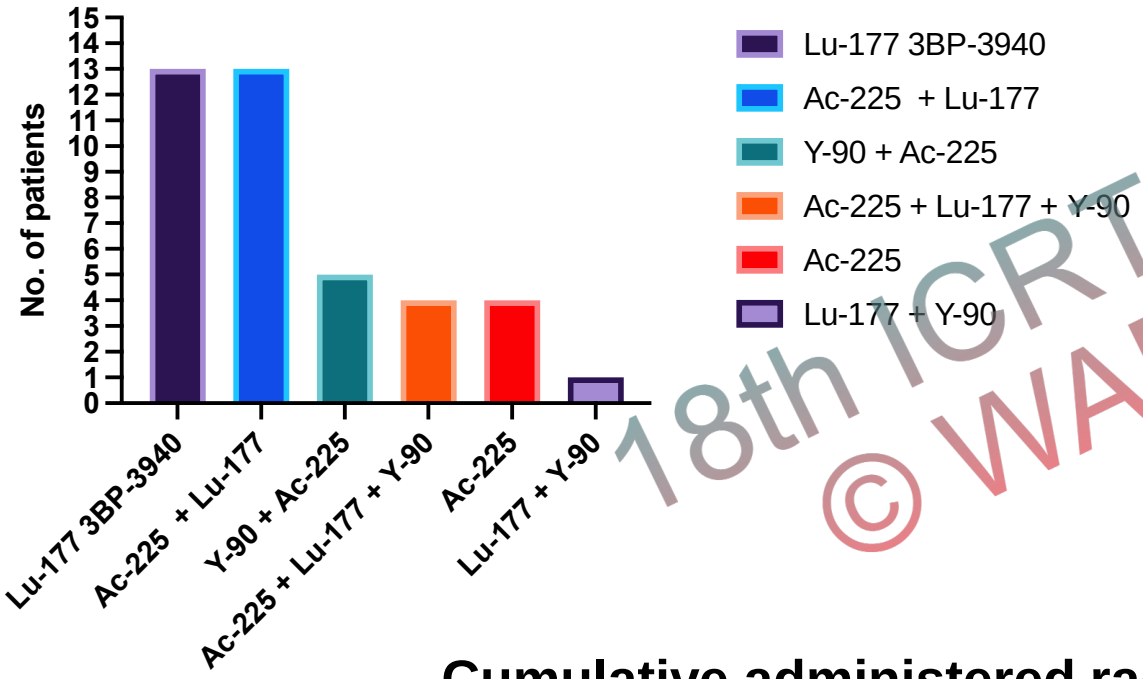
Swimmer plot of previous treatments & 3BP-3940 PTRT



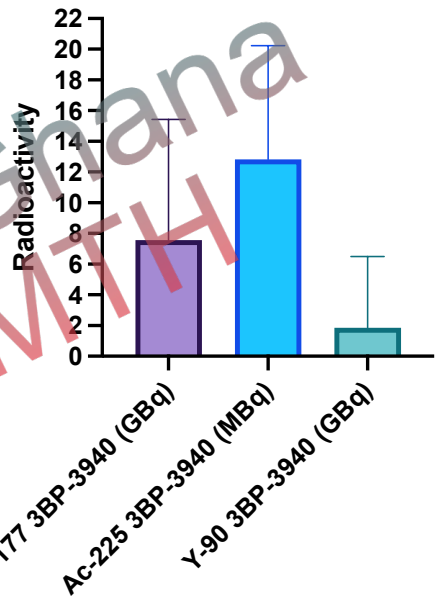
EBRT (external beam radiation therapy)**, PTRT** (peptide-targeted radionuclide therapy)

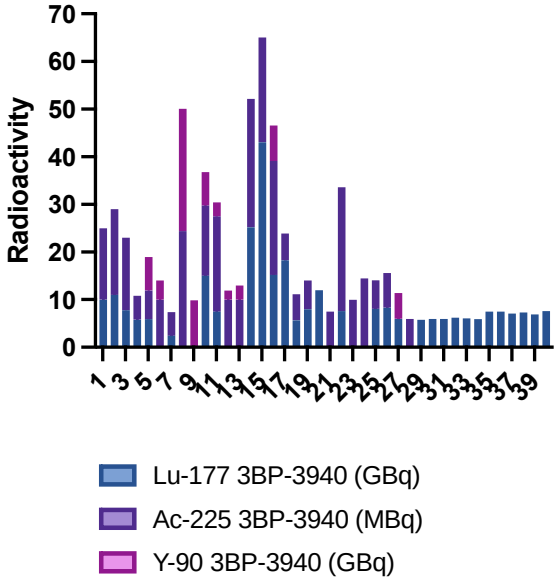
PTRT using 3BP-3940 – cumulative dosage

Types: ^{177}Lu- / ^{177}Lu+^{225}Ac / ^{90}Y+^{225}Ac / ^{90}Y PTRT



Cumulative Radioactivity per Patient (n = 40)





Cumulative administered radioactivity per patient

- ^{225}Ac-FAP-3BP-3940 - 12.83 ± 7.41 MBq; range 5.0 – 33.0 MBq
- ^{177}Lu-FAP-3BP-3940 - 9.77 ± 7.63 GBq; range 2.4 – 43.1 GBq
- ^{90}Y-FAP-3BP-3940 - 7.44 ± 6.89 GBq; range 1.9 – 25.7 GBq

PATIENTS' CHARACTERISTICS PTRT (PEPTIDE-TARGETED RADIONUCLIDE THERAPY

Pt	Age (y)	Gender	Primary tumor	Metastases	Genetics	SX	CHX	EBRT	IMT	HX*	PTRT cycles	Cumulative activity (FAP)			THERCIST (PET results)	Survival since 1st PTRT (months)
												Lu-177 GBq	Ac-225 MBq	Y-90 GBq		
1	56	M	Oropharynx (SCC)	LNM, OSS, PUL	No	Yes	Yes	Yes	Yes		2	10	15		MR	3 †
2	63	M	Prostate carcinoma (SCC/neuroendocrine)	LNM, OSS, HEP	No	No	Yes	Yes	Yes	Yes	2	10.8	18		MR	2 †
3	73	M	Pancreas ductal adenocarcinoma	HEP	No	Yes	Yes	No	No		2	7.8	15.2		PD	4 †
4	54	M	Thymus neuroendocrine neoplasia	LNM, OSS, PUL, CAR	-ND	Yes	Yes	Yes	Yes		1	5.8	5		PD	3 †
5	57	M	Pancreas ductal adenocarcinoma	HEP, PUL, PER, ST	-ND	No	No	No	No		3	8.1	20.6	7.1	SD	8 †
6	72	F	Sarcoid-like ovary adenocarcinoma	LNM, OSS, PUL, ST	No	Yes	Yes	No	No		1	4	10		PD	13 †
7[a]	69	M	Atypical lung carcinoid	OSS, PUL, ST	No	No	No	Yes	No		1	2.4	5		PD	12 †
8	60	F	Epithelioid pancreatic carcinoma	HEP, GE	Yes	Yes	Yes	Yes	Yes		4		24.4	25.7	PR	7 †
9	58	M	Esophageal cancer	LNM, HEP	No	No	No	No	Yes		2		10	9.9	PD	15 †
10[b]	37	F	Clear cell sarcoma of the small intestine	LNM, HEP, GE, PER	-ND	Yes	Yes	No	No		4	7.5	26.3	14	PD	14 †

LNM (lymph node metastases), **OSS** (bone), **PUL** (pulmonary), **GE** (gastroenteral), **HEP** (liver), **PER** (peritoneal), **CAR** (cardiac), **ST** (soft tissue), **BR** (brain), **SUR** (surgery), **CHE** (chemotherapy), **RLT** (radioligand therapy), **EBRT** (radiation therapy), **IMT** (immunotherapy), **HX** (hormonal therapy – where applicable)

[a] received two PRRT cycles with Lu-177 DOTATOC (15.5 GBq), [b] received TACE (CHE)

Pt	Age (y)	Gender	Primary tumor	Metastases	Genetics	SX	CHX	EBRT	IMT	HX*	PTRT cycles	Cumulative activity (FAP)			THERCIST (PET results	Survival since 1st PTRT months
												Lu-177 GBq	Ac-225 MBq	Y-90 GBq		
11[c]	67	M	Prostate carcinoma	ST, LNM, OSS, HEP	Yes	Yes	Yes	Yes	No	Yes	1		10	1.9	PD	10 †
12[d]	76	M	Prostate carcinoma	Perirectal growth	Yes	Yes	No	No	No	No	1	7.8	10	3	SD	17 alive
13	50	F	Breast cancer (DCIS) very advanced	PER, LNM, OSS, HEP	Yes	Yes	Yes	No	No	Yes	2	7.5	20	2.9	PR	2.5 †
14	60	F	Pancreas ductal adenocarcinoma	HEP, LNM	Yes	Yes	Yes	Yes	No		4	33.4	33		PR	11 †
15	53	F	Pancreas ductal adenocarcinoma	HEP, PER, OSS	Yes	No	Yes	No	Yes		5	43.1	22.4		PD	14 †
16[e]	57	F	Pancreas ductal adenocarcinoma	HEP, ST	ND	No	Yes	No	Yes		5	31.7	23.9	7.5	PD	7.5 †
17[f]	52	F	Ovarian adenocarcinoma	LNM	Yes	Yes	Yes	No	Yes	No	3	27.6	5.6		CR	13 alive
18[g]	43	F	Breast cancer	HEP, OSS, LNM, pleural	Yes	Yes	Yes	No	Yes	Yes	1	5.7	5.5		PD	2 †
19	46	M	Pancreas NET	LNM, OSS	No	No	Yes	Yes	No		1	8	6		PR	1 †
20	36	F	Tripple negative breast cancer	LNM, PUL, HEP, OSS, BR, ST	Yes	Yes	Yes	Yes	Yes	Yes	1	12			PD	1 †

LNM (lymph node metastases), **OSS** (bone), **PUL** (pulmonary), **GE** (gastroenteral), **HEP** (liver), **PER** (peritoneal), **CAR** (cardiac), **ST** (soft tissue), **BR** (brain), **SUR** (surgery), **CHE** (chemotherapy), **RLT** (radioligand therapy), **EBRT** (radiation therapy), **IMT** (immunotherapy), **HX** (hormonal therapy – where applicable)

[c] Patient received 10 cyles PSMA-PRLT before (OS since start of radioligand therapy – 52 months)

[d] Patient received 2cycles PSMA-PRLT before

[e] Patient received additional immune checkpoint inhibitor therapy together with the 5th PTRT

[f] presence of second and third primary (bilateral breast cancer)

[g] Pat. died of sepsis after immune checkpoint inhibitor therapy

Pt	Age (y)	Gender	Primary tumor	Metastases	Genetics	SX	CHX	EBRT	IMT	HX*	PTRT cycles	Cumulative activity (FAP)			THERCIST (PET results	Survival since 1st PTRT [months]
												Lu-177 GBq	Ac-225 MBq	Y-90 GBq		
21	52	F	Colon cancer	LNM, OSS, HEP, PUL, BR	Yes	Yes	Yes	No	Yes		1		7.5		PD	0[h]
22	60	M	Lung (NSCLC) adenocarcinoma	PUL, OSS, mediastinum	No	No	Yes	Yes	No		3	7.6	13		PD	2.5 †
23[i]	58	M	Appendix (signet ring cell adenocarcinoma)	LNM, PUL, PER	Yes	Yes	Yes	No	Yes		1		19		PD	3.5 †
24	59	M	Pancreas ductal adenocarcinoma	LNM, PER, HEP	No	No	Yes	No	No		3	7	29.5		PD	7 †
25	72	F	Ureter (urothelial carcinoma)	LNM, HEP, OSS	No	Yes	No	No	No		3	15	6		PR	8 alive
26	51	M	Lung adenocarcinoma (NSCLC)	LNM, PER, PUL	Yes	No	Yes	No	No		4	19	7.3		PR	8 alive
27	66	M	Liver (sarcomatoid hepatocellular carcinoma)	OSS, ST	Yes	Yes	No	Yes	No		4	19.1		5.4	PR	7 alive
28[j]	76	M	Lung (NSCLC) adenocarcinoma	LNM, OSS, BR	Yes	No	Yes	Yes	Yes		3	18.4			PR	5 alive
29	56	F	Pancreas ductal adenocarcinoma	LNM, HEP, ST, PUL	Yes	Yes	Yes	Yes	No		1	5.8			PD	3 †
30	70	M	Colon adenocarcinoma	PER, HEP, ST	Yes	Yes	Yes	No	Yes		2	13.2			PR	5 alive

LNM (lymph node metastases), **OSS** (bone), **PUL** (pulmonary), **GE** (gastroenteral), **HEP** (liver), **PER** (peritoneal), **CAR** (cardiac), **ST** (soft tissue), **BR** (brain), **SUR** (surgery), **CHE** (chemotherapy), **RLT** (radioligand therapy), **EBRT** (radiation therapy), **IMT** (immunotherapy), HX (hormonal therapy – where applicable)

[h] Patient died on day 2 after therapy due to lung emboli

[i] Patient received additional Immuncheckpoint-Inhibitor Therapy with the 1st PTRT. Pat. died post bowel bypass surgery.

[j] NSCLC was discovered during PSMA PET/CT restaging of known prostate cancer

Pt	Age (y)	Gender	Primary tumor	Metastases	Genetics	SX	CHX	EBRT	IMT	HX *	PTRT cycles	Cumulative activity (FAP)			THERCIST (PET results	Survival since 1st PTRT [months]
												Lu-177 GBq	Ac-225 MBq	Y-90 GBq		
31	37	F	Tripple negative breast cancer	LNM, HEP, PER	Yes	Yes	Yes	No	Yes		3	18.2			PR	5 alive
32	60	M	Lung (NSCLC) adenocarcinoma	OSS	Yes	Yes	Yes	No	No		3	19.4	3.5		PR	4 alive
33k	78	F	Signet ring cell carcinoma (CUP)	LNM, OSS	No	No	Yes	Yes	No		1	6.1			PD	3 alive
34	64	F	Pancreas adenocarcinoma	OSS, HEP	No	Yes	Yes	No	No		2	13			MR	3 alive
35	65	F	Breast cancer	LNM, OSS, PUL, HEP	No	No	Yes[l]	No	No		2	15.1			PR	3 alive
36	65	M	Esophageal carconima	LNM, OSS, HEP, pancreas	Yes	No	Yes	Yes	Yes		3	21	3.5		PR	3 alive
37	80	M	Esophageal leiomyosarcoma	HEP, PER, ST	Yes	Yes	No	Yes	No		2	13.1			SD	3 alive
38	57	M	Uveal melanoma	HEP	No	No	Yes[m]	No	No		2	13.3			PD	3 alive
39	60	F	Breast cancer	LNM, PUL	Yes	Yes	Yes[k]	Yes	No		2	12.9	3.5		PD	2 alive
40	57	F	Pancreas adenocarcinoma	LNM, HEP, PER	Yes	Yes	Yes	No	No		2	15.8			PR	2 alive

LNM (lymph node metastases), **OSS** (bone), **PUL** (pulmonary), **GE** (gastroenteral), **HEP** (liver), **PER** (peritoneal), **CAR** (cardiac), **ST** (soft tissue), **BR** (brain), **SUR** (surgery), **CHE** (chemotherapy), **RLT** (radioligand therapy), **EBRT** (radiation therapy), **IMT** (immunotherapy), HX (hormonal therapy – where applicable)

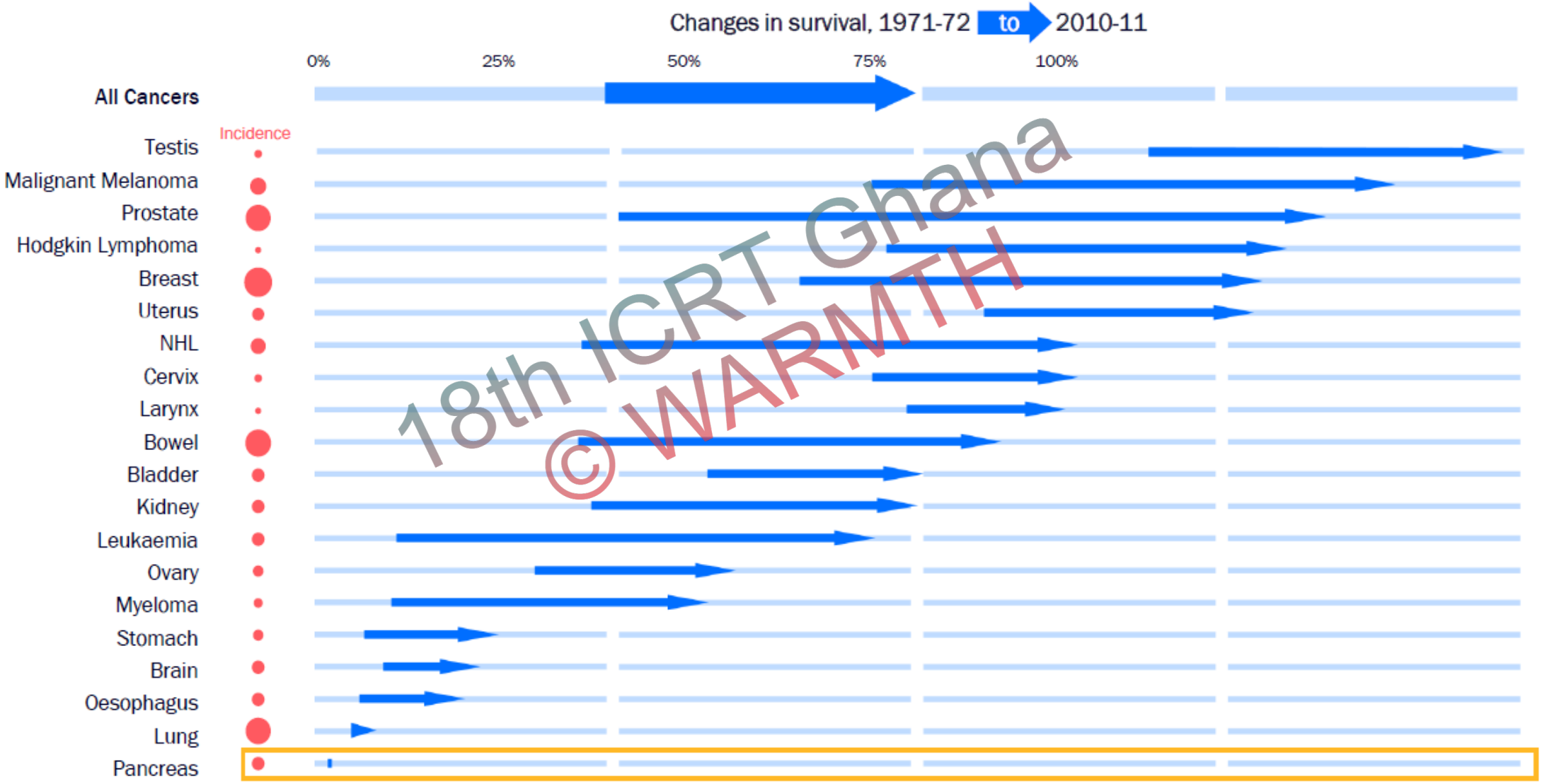
[k] 2nd tumor – breast cancer (in remission) [l] hormone therapy [m] TACE

Pt	Age (y)	Gender	Primary tumor	Metastases	Genetics	SX	CHX	EBRT	IMT	HX *	PTRT cycles	Cumulative activity (FAP)			THERCIST (PET results	Survival since 1st PTRT [months]
												Lu-177 GBq	Ac-225 MBq	Y-90 GBq		
41	67	M	Urothelial carcinoma	LNM	No	Yes	Yes	No	No		1	3.7			PD[n]	2
42	53	M	Rectum Adenocarcinoma	HEP	No	Yes	Yes	Yes	Yes		1	6			PD	2
43	64	F	Pancreas ampullary adenocarcinoma	LNM	Yes	Yes	Yes	No	Yes		1	5.9	3.5		PD	1
44[m]	48	F	Breast cancer	LNM	Yes	Yes	Yes	Yes	Yes	Yes	1	6	3.5		PD	1
45	52	M	Esophageal adenocarcinoma	LNM, HEP, adrenal gland	Yes	No	Yes	Yes	Yes		1	8.2			PD	1

LNM (lymph node metastases), **OSS** (bone), **PUL** (pulmonary), **GE** (gastroenteral), **HEP** (liver), **PER** (peritoneal), **CAR** (cardiac), **ST** (soft tissue), **BR** (brain), **SUR** (surgery), **CHE** (chemotherapy), **RLT** (radioligand therapy), **EBRT** (radiation therapy), **IMT** (immunotherapy), HX (hormonal therapy – where applicable)

[n] Staging with Ga-68 CXCR4 PET/CT; intravesical PTRT [m] also has pancreatic adenocarcinoma & papillary thyroid carcinoma

The prognosis for pancreatic cancer patients has remained almost unchanged for over 40 years[1] with a reported five-year survival rate for the disease of 10%[2]



References: 1. Cancer Research UK. www.cancerresearchuk.org/health-professional/cancer-statistics/survival/common-cancers-compared#heading-Three (accessed November 2021)
2. American Cancer Society. Cancer Facts & Figures 2021. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf

Pancreatic INI1-deficient undifferentiated rhabdoid carcinoma achieves complete clinical response on gemcitabine and nab-paclitaxel following immediate progression on FOLFIRINOX: a case report

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Journal of Gastrointestinal Oncology, Vol 12, No 2 April 2021

ONCOLOGIC DIAGNOSIS (60-Y-OLD WOMEN)

1. INI-1 deficient poorly differentiated epithelioid pancreatic carcinoma with disseminated liver metastases and stomach infiltration

Histologic diagnosis established in March 2019

Tumor classification pT1c pN1 cM0, initial tumor stage IIb

STAMP: KRAS G12D

Pathology (April 2019): PD-L1 positive CPS = 20 (Caris: No actionable mutations, PDL-1 negative)

Invitae (May 2020): No mutations (108 genes tested), Guardant 360 (17-Jun-20): KRAS mutation at 0.1 %

HISTORY OF PRESENT ILLNESS

26-Mar-2019	Abdominal and back pain (initial symptoms); hypodense lesions in pancreas and liver (CT)
27-Mar-2019	Heterogeneous solid/cystic lesion in the body of the pancreas (1.7 x 1.3 cm) on MRI
28-Mar-2019	Diagnosis established (EUS guided FNA of the pancreatic mass)
15-Apr-2019	Hypermetabolic pancreatic body tumor (1.8 cm) - FDG PET/CT (Stanford)
22-Apr-2019	Robotic distal pancreatectomy with celiac lymphadenectomy (pT1c pN1 cM0)
05-06/2019	Progressive hepatic lesions (CT)
06-07/2019	Chemotherapy with FOLFIRINOX (3 cycles); progressive hepatic metastases (CT)
07/19 – 03/20	Chemotherapy with Gemcitabine + nab-Paclitaxel– 8 cycles; **excellent response (CR)**
27-May-2020	Phase 1 mRNA KRAS vaccine, HLA not eligible (UCSF)
30-Oct-2020	Progression - new mass, gastro-hepatic ligament protruding in the gastric lumen (CT)
11/20 – 04/21	Therapy with selective EZH2 inhibitor TAZVERIK (Tazemetostat)
11/20-05/21	Renewed chemotherapy with Gemcitabine + nab-Paclitaxel
08-Dec-2020	Started CeGAT's neo-epitope vaccine (monthly)
12/20 – 05/21	Immunotherapy with Pembrolizumab (6 courses)
01-04/2021	Progressive liver metastases (multiple CT scans and FDG PET/CT – 2 studies)
15-Apr-2021	Stomach lesion biopsy, sent for organoid & PDX evaluation

05/2021 MRI-guided external beam radiation therapy of para-gastric area and pancreas (UCLA)
09-Jul-2021 Progression of the disease (Ga-68 FAP PET/CT)
18-Aug-2021 Trans-arterial chemoembolization (TACE)
01-Sep-2021 **Initiation of Peptide-Targeted Radionuclide Therapy (PTRT)**
20-Oct-2021 Regression of liver metastases (CT)

2. Left clival (skull base) chondrosarcoma

S/p resection and proton beam therapy in 2013

PAST MEDICAL HISTORY / ACCOMPANYING DISEASES

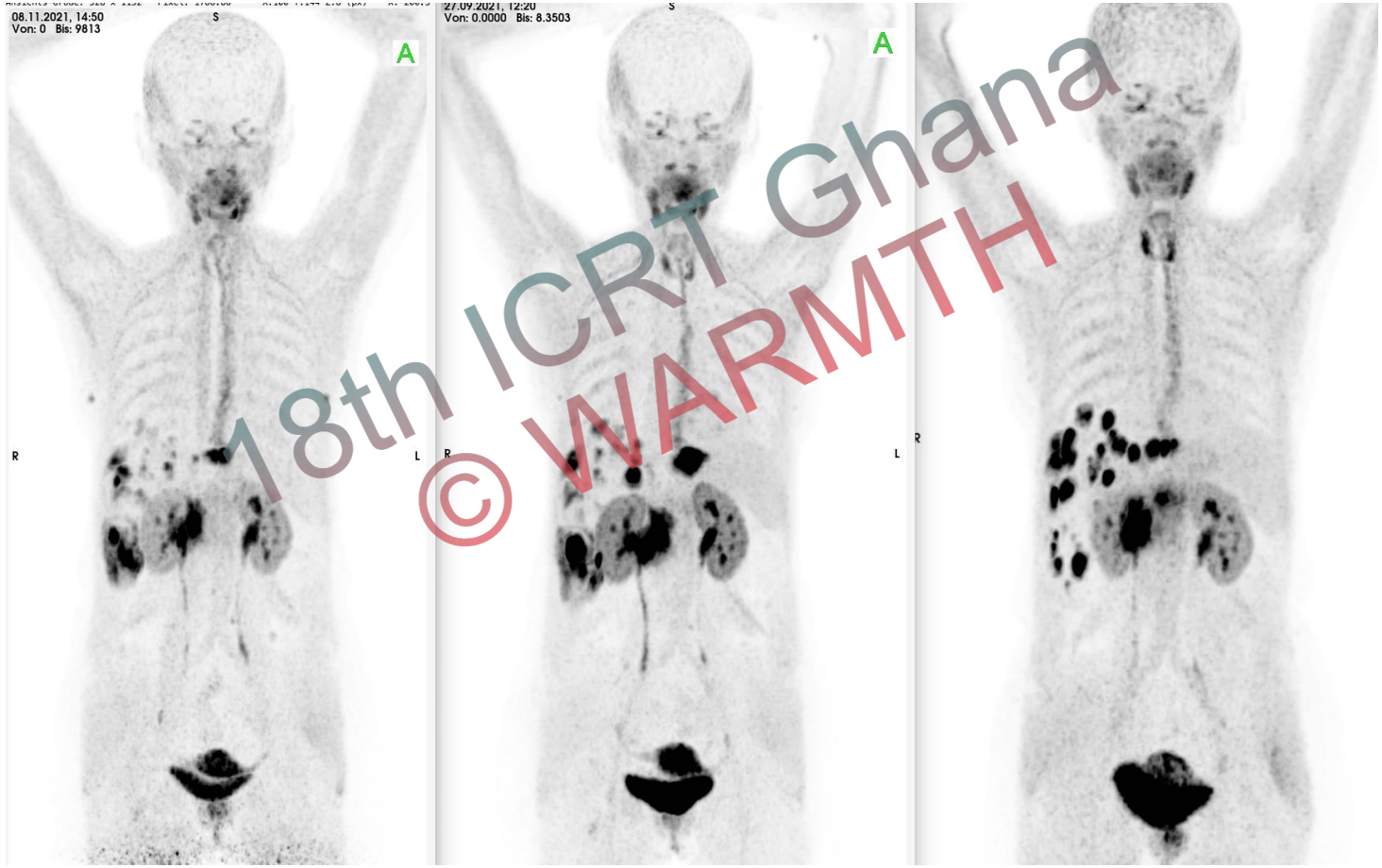
Anemia grade 2 (before PTRT) – currently pancytopenia grade 1,
diabetes mellitus (pancreoprive), HbA1c 5.2% on oral anti-diabetics

PEPTIDE-TARGETED RADIONUCLIDE THERAPY (PTRT)

01-Sep-2021: PTRT with **5 GBq Y-90 / 17 MBq Ac-225 3BP-3940** (1st cycle)
29-Sep-2021: PTRT with 7.6 GBq Y-90 3BP-3940 (2nd cycle)
08-Nov-2021: PTRT with 7.0 GBq Y-90 3BP-3940 (3rd cycle)
Cumulative administered radioactivity 19.6 GBq of Y-90 3BP-3940 / 17 MBq Ac-225 3BP-3940

Metastatic Pancreas Adeno Ca

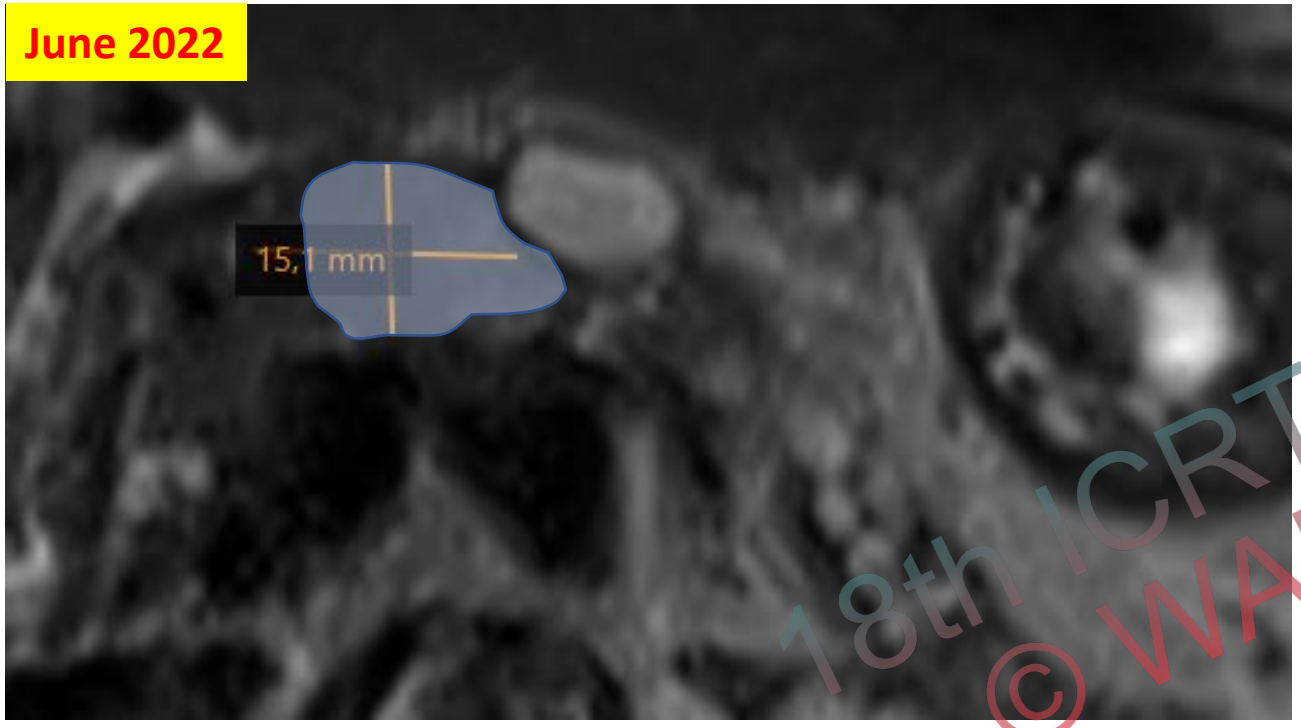
PET /CT follow up using ^{68}Ga-3BP-3940

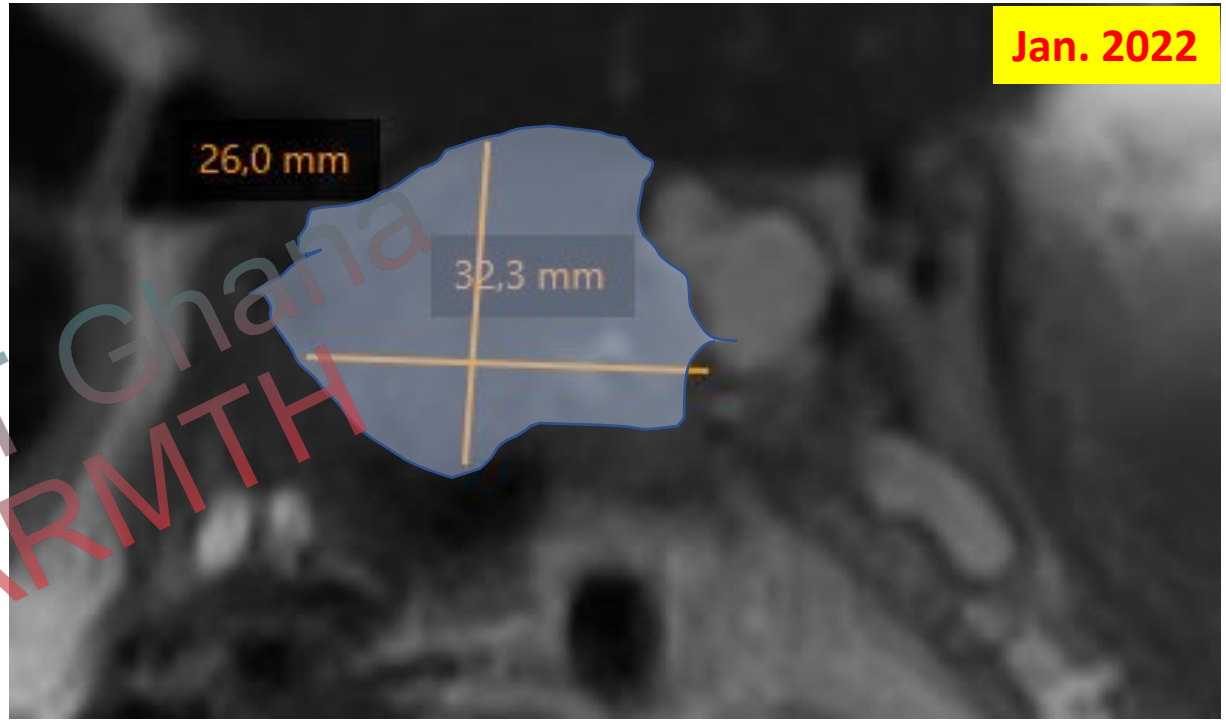


Feb 2022 Dec 2021 Oct 2021

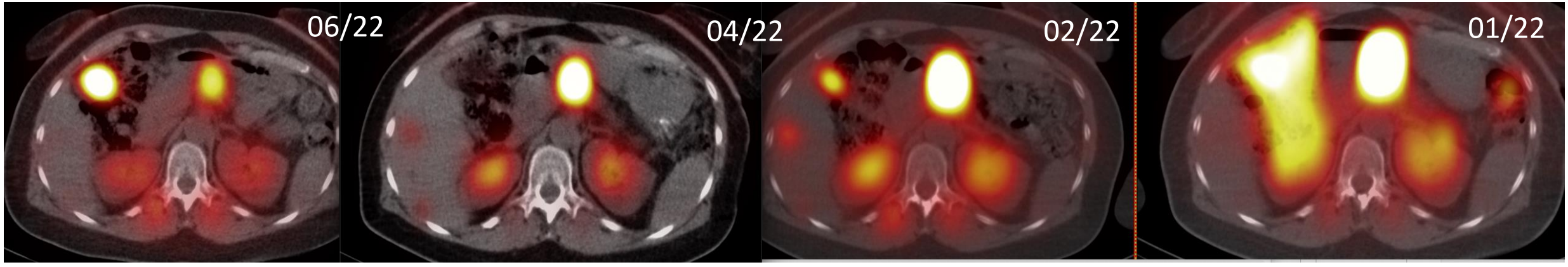
Pancreatic ductal adenocarcinoma (metastatic PDAC)

MRI pre/post PTRT: Objective response according to RECIST

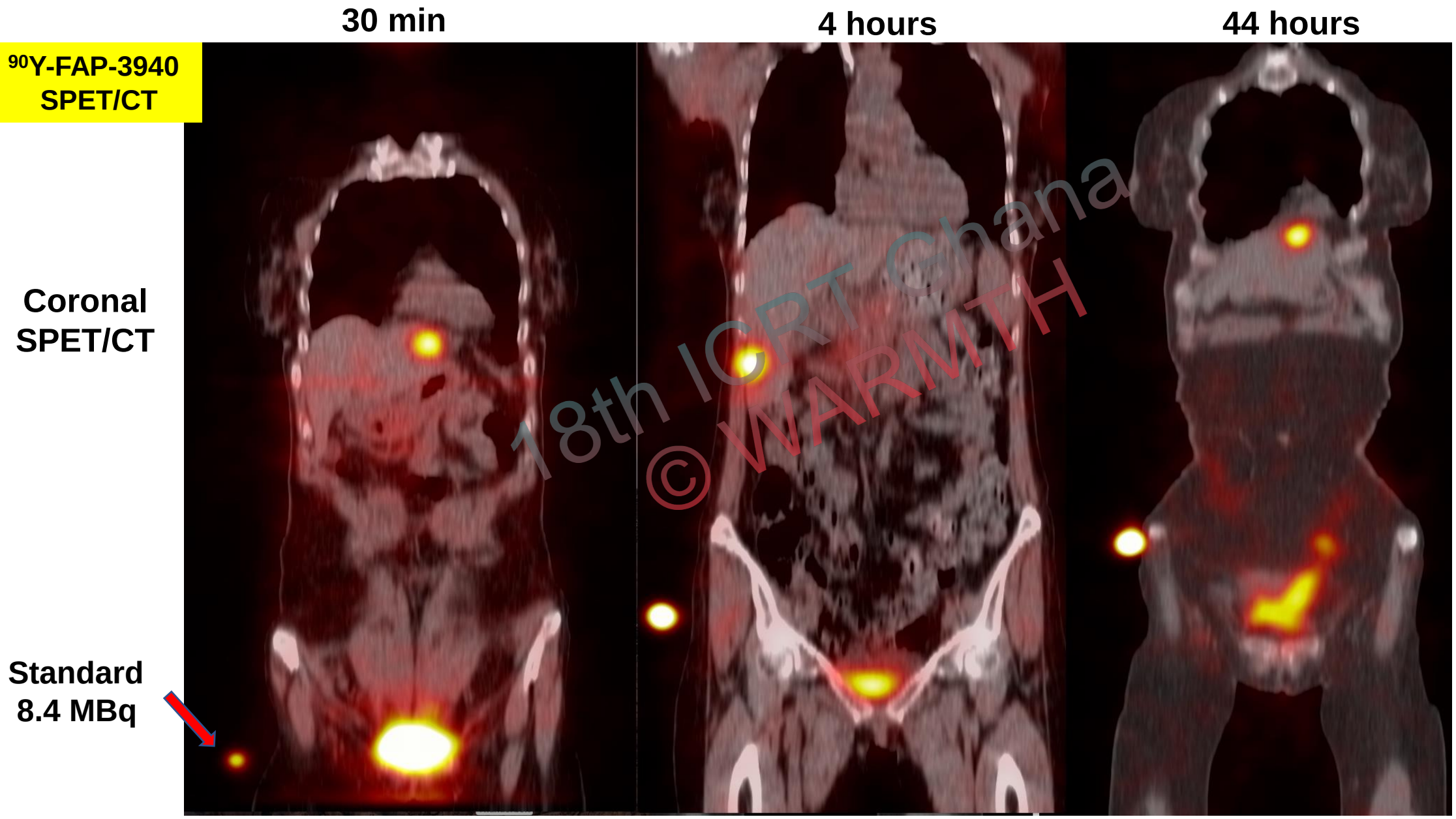


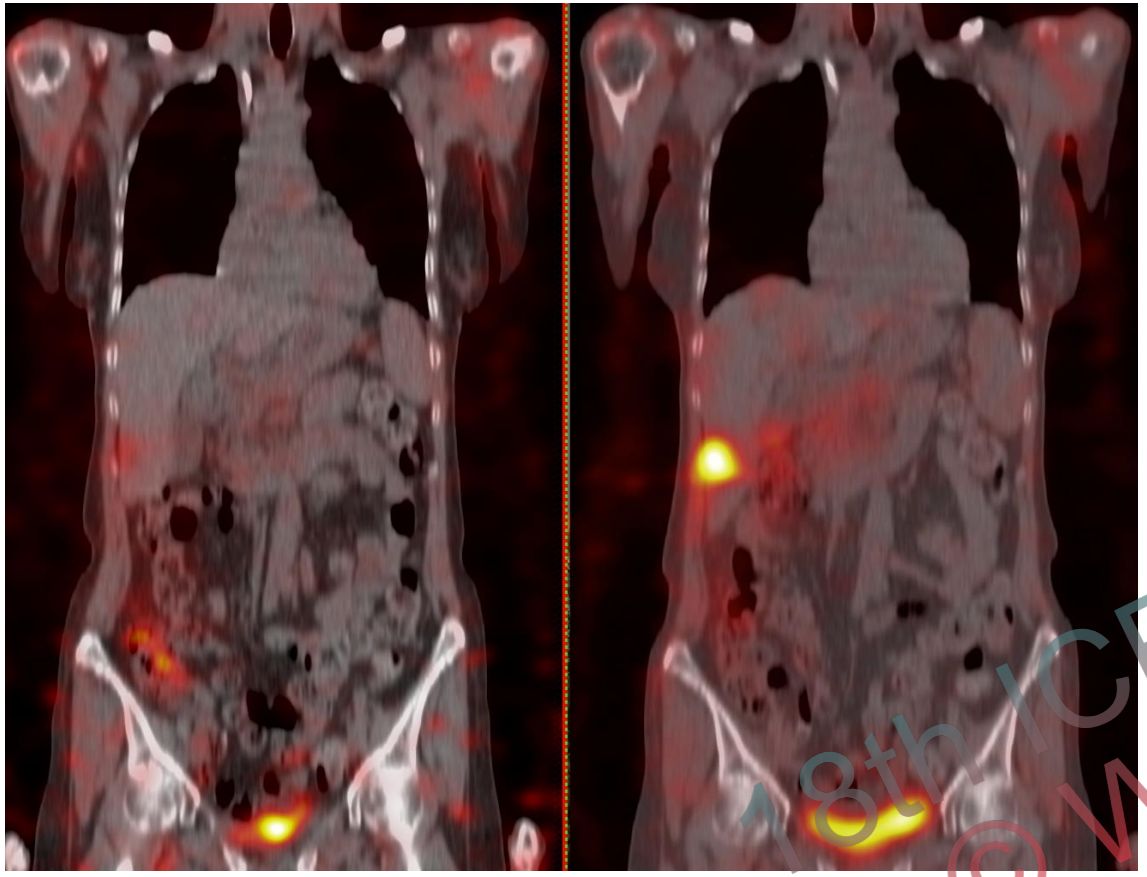


^{177}Lu-3BP-3940 SPET/CT under PTRT: decreasing uptake on molecular imaging (THERCIST)



Pancreatic adenocarcinoma, liver metastases
PTRT with 7.6 GBq of Yttrium-90 3BP-3940 peptide





08-Nov-2021

29-Sep-2021

08-Nov-2021

29-Sep-2021

^{90}Y-3BP-3940 SPET/CT

Reponse to PTRT (2 cycles) according to molecular imaging criteria

SEP 1st, 2021

2 weeks after TACE

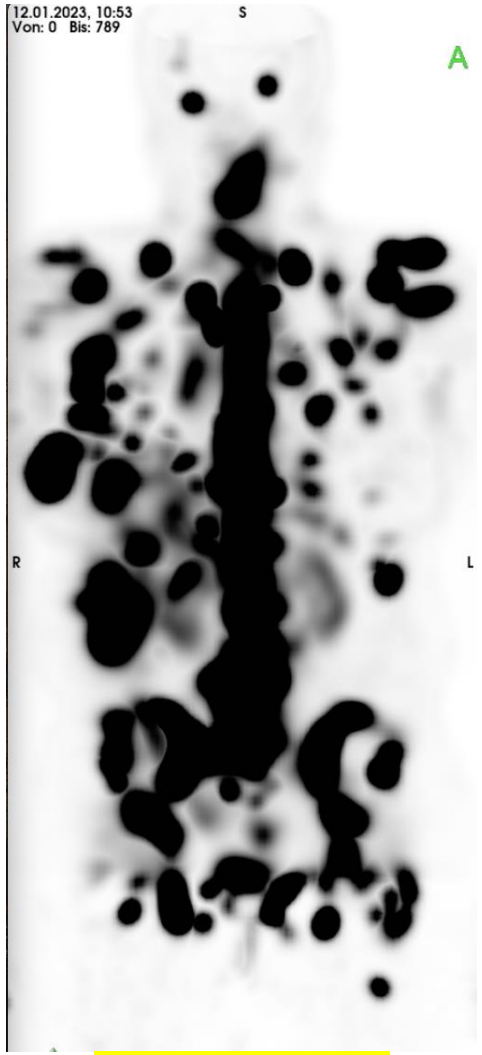
3 h after 5 GBq ^{90}Y-3BP-3940

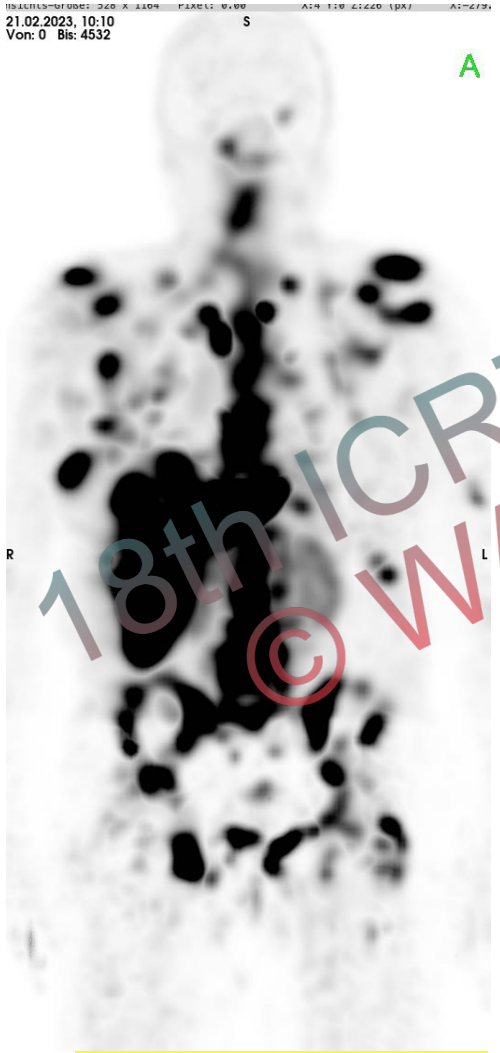
plus

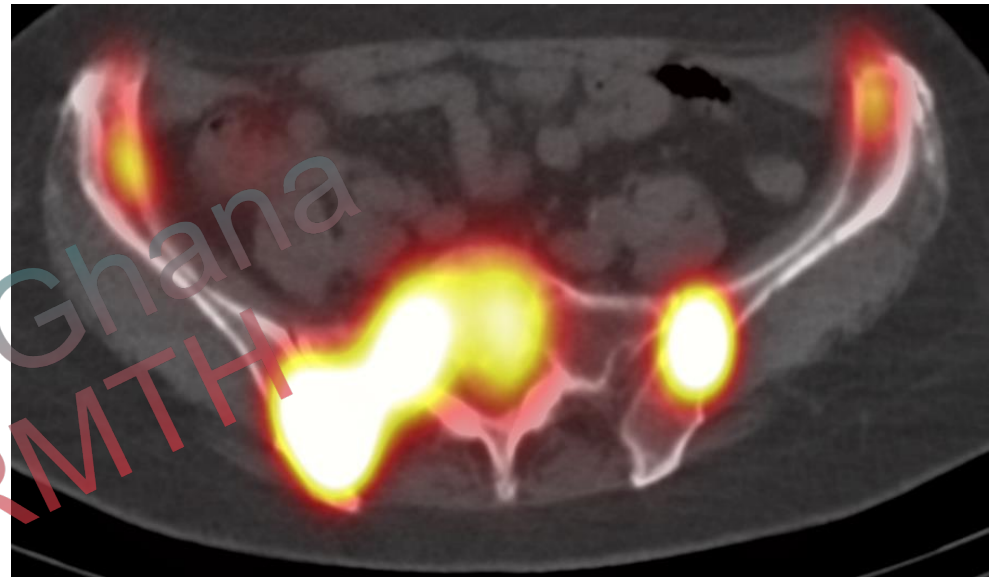
17 MBq ^{225}Ac-3BP 3940

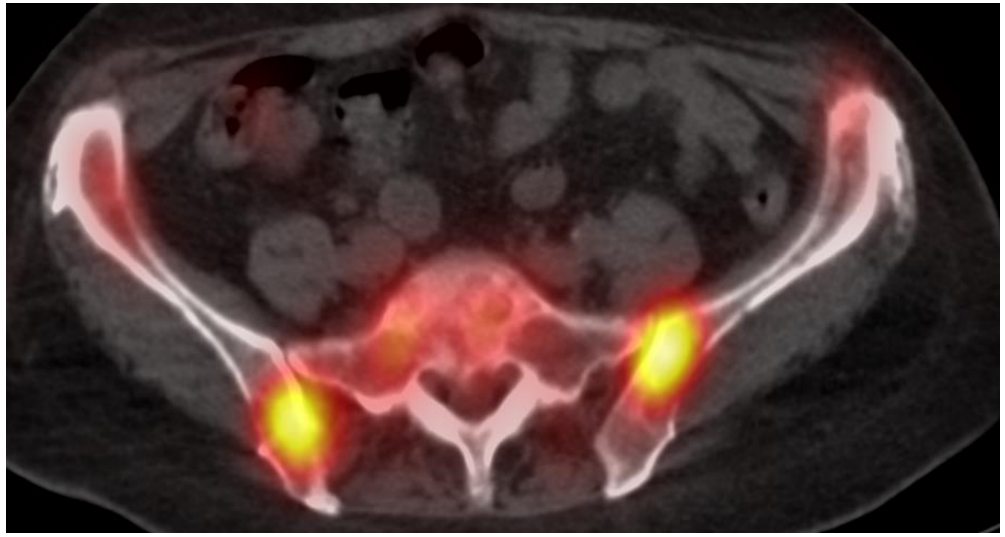
^{90}Y-3BP-3940 SPET/CT

Primary breast cancer with disseminated metastases treated with one cycle *de novo* ^{177}Lu-3BP-3940









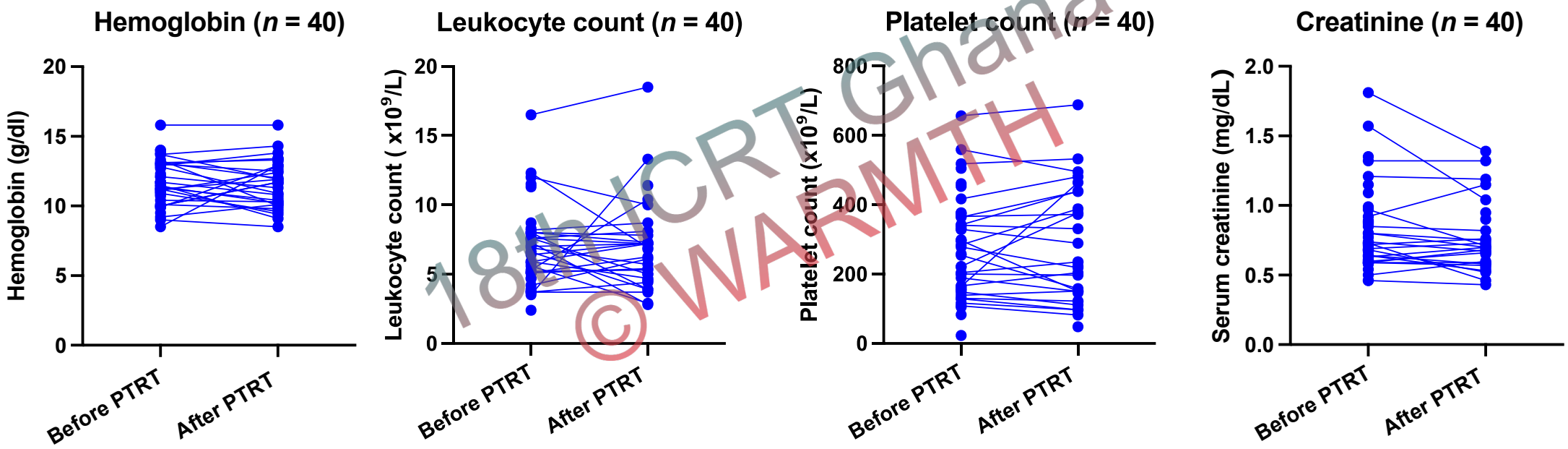
before PTRT

after 1 cycle PTRT

No clinically relevant adverse effects one bone marrow or renal function

Blood counts / creatinine before and after PTRT using 3BP-3940

Comparison of hemoglobin, leukocytes, platelets, and serum creatinine) before therapy and after 1-4 cycles of PTRT



- New anemia occurred after PTRT in 6 patients (from G1 to G2 in 4 Pts, from G0 to G1 in 2 Pt). However, HB improvement was observed in 3 patients (from G2 to G1). New leukocytopenia occurred after PTRT in 2 patients (G1).
- Grade 3 or 4 anemia, leukocytopenia, and thrombocytopenia occurred in 0 Pt, 0 Pt, and 1 Pt, respectively.
- No renal toxicity occurred after PTRT. Even the elevated creatinine was decreased after PTRT in 1 patient - no significant change in renal parameters in other patients.
- No adverse effects or clinically detectable pharmacologic effects were noticed or reported in any of the patients.

Oncological diagnosis

1. **Poorly differentiated focal papillary, solid serous, partly cystic adenocarcinoma of the ovary, Initial tumor classification pT2c pN0 M0 L1 V0 Rx G3, stage Ic, initial diagnosis 01/2010**

01/2010	Elevated tumor markers (screening); histological confirmation (laparoscopy)
02/04/2010	Laparoscopy, bilateral adnexectomy
02-09-2022	Hysterectomy with paraaortic lymphnodectomy and omentectomy
03-06/2010	6 courses of chemotherapy with carboplatin and paclitaxel
10/2021	Clinical disease progression - left inguinal pain
12/2021	Extensive mass (Ø 4.5 cm) in the left pelvis, obstruction of left ureter, hydronephrosis
012022	Local recurrence with multiple lymph node metastases (Ga-68 FAPI PET/MRI)
02-10/2022	Local recurrence with multiple lymphonodular metastases (Ga-68 FAP-3940 PET/CT)
02-03/2022	2 courses of chemotherapy with carboplatin and paclitaxel
	3 courses of immunotherapy with bevacizumab (anti-VEGF, Avastin®)
03/2022	**Initiation of FAP-mediated radiopeptide therapy (PTRT)**

PEPTIDE-TARGETED RADIONUCLIDE THERAPY (PTRT)

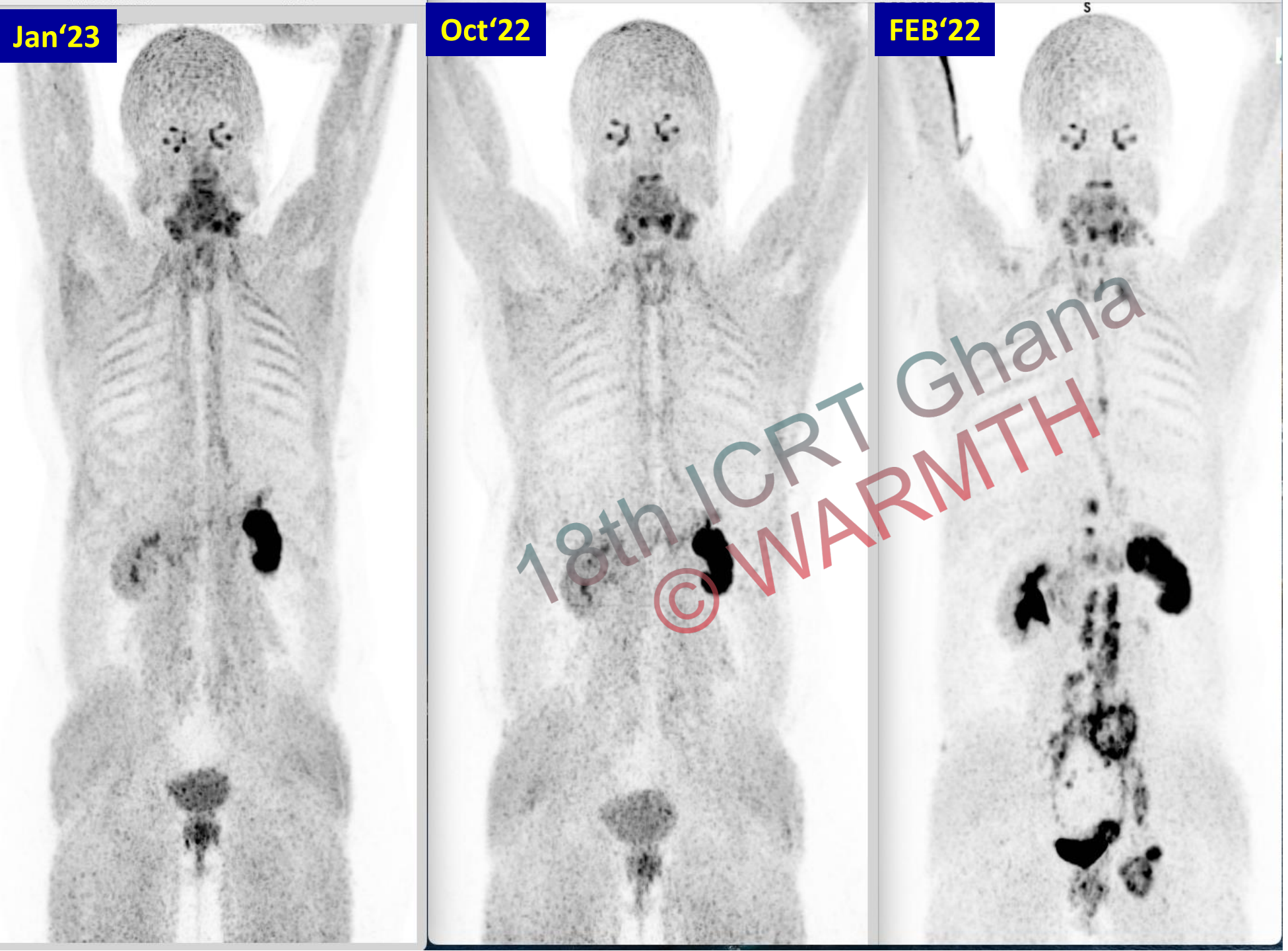
PTRT with 7.6 GBq Lutetium-177 and **5.6 MBq Actinium-225 FAP-3940** (1st cycle PTRT)
PTRT with 10.7 GBq Lutetium-177 FAP-3940 (2nd cycle PTRT)
PTRT with 9.3 GBq Lutetium-177 FAP-3940 (3rd cycle PTRT)
Cumulative administered radioactivity 27.6 GBq Lu-177 / 5.6 MBq Ac-225

Continuation of chemotherapy until August 2022 and of immunotherapy until currently

2. Moderately differentiated multifocal invasive ductal triple negative breast carcinoma right, FD 2005
Initial tumor classification pT2 pN0(0/14) G2
29.03.2005 Breast conserving surgery with axillary lymphonodectomy
04. 04.2005 Ablatio mammae right
04-08/2005 6 courses chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide)
2008 Deep Inferior Epigastric Perforator (DIEP) flap surgery right

3. Moderately differentiated triple-negative breast carcinoma (TNBC) left, FD 09/2014
Initial tumor classification cT1c pN0 G2 Proliferation index (Ki67): 80%
12.09.2014 Histological backup (punch biopsy left)
10-11 /2014 2 courses of chemotherapy with carboplatin/paclitaxel
11/14-01/15 6 courses of chemotherapy with cisplatin/paclitaxel (due to allegy against carboplatin)
02/2015 Mastectomy left (ypT0 R0), implant reconstruction

<u>Concomitant diseases / associated diagnoses</u>
Ascites, non-functional shrunken kidney on the left (outflow obstruction due to tumor-related compression of the left ureter) - current serum creatinine 0.99 mg/dl, post appendectomy (1978), osteochondrosis, allergy to carboplatin, povidone-iodine and patch adhesive

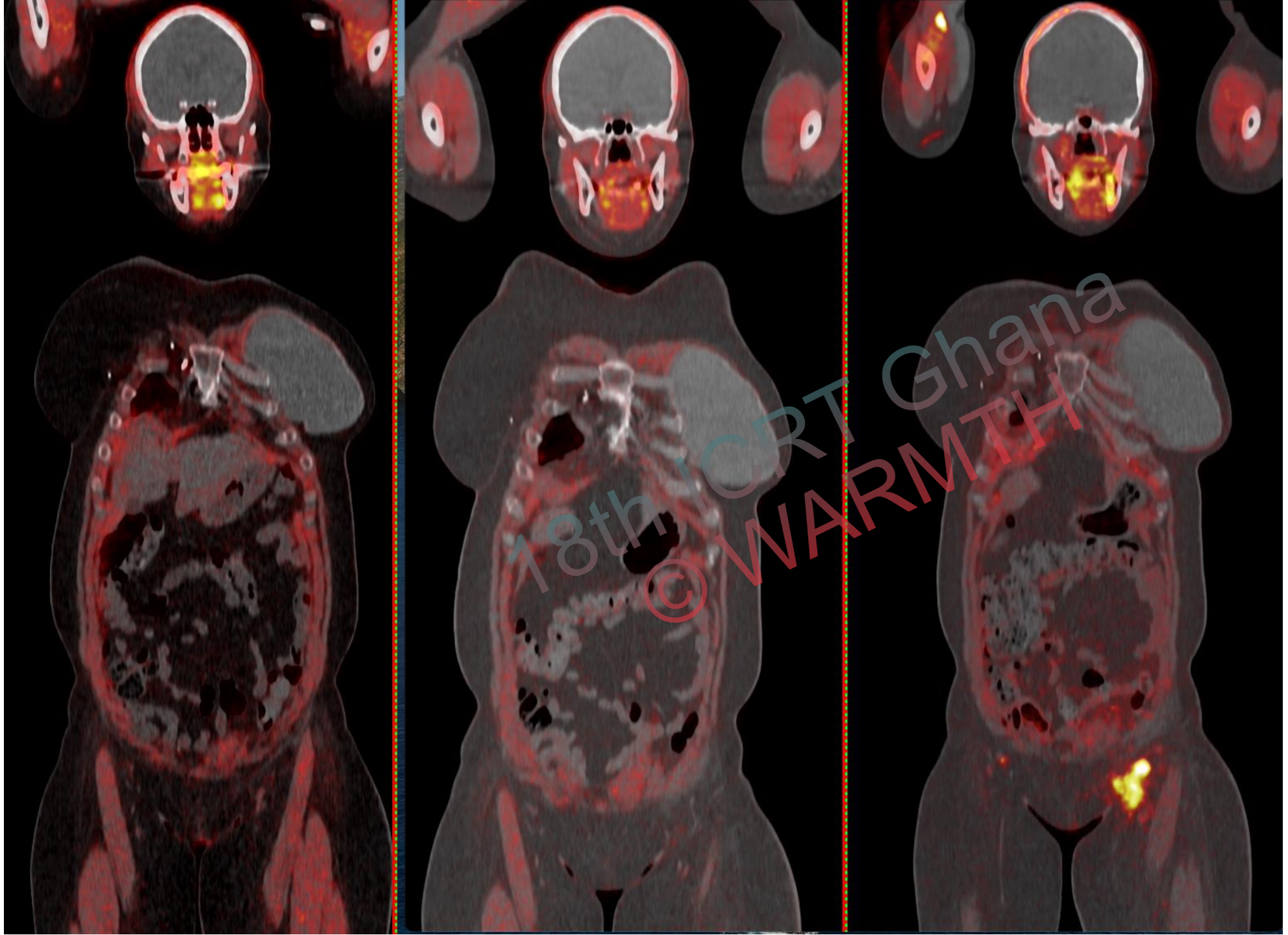


Ovarian Cancer

(extensive lymph node metastases)

Baseline,
and
9 and 12
months
follow-up

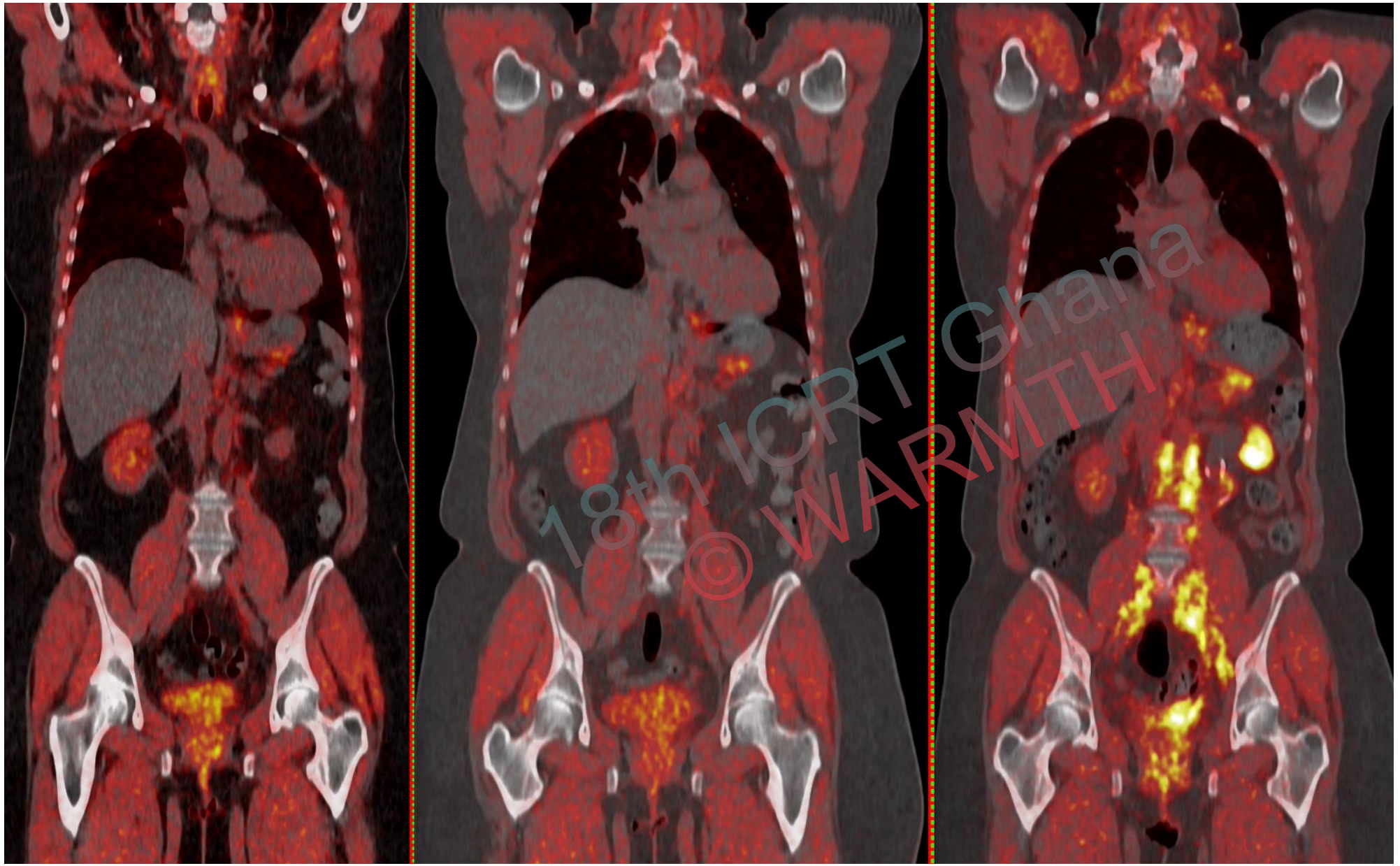
^{68}Ga-3BP-3940
FAP
MIP images



Ovarian Cancer
(inguinal lymph node metastases)

Baseline,
and
9 and 12
months
follow-up

^{68}Ga-3BP-3940
FAP
coronal images



Ovarian Cancer

(retroperitoneal lymph node metastases)

Baseline, and 9 and 12 months follow-up

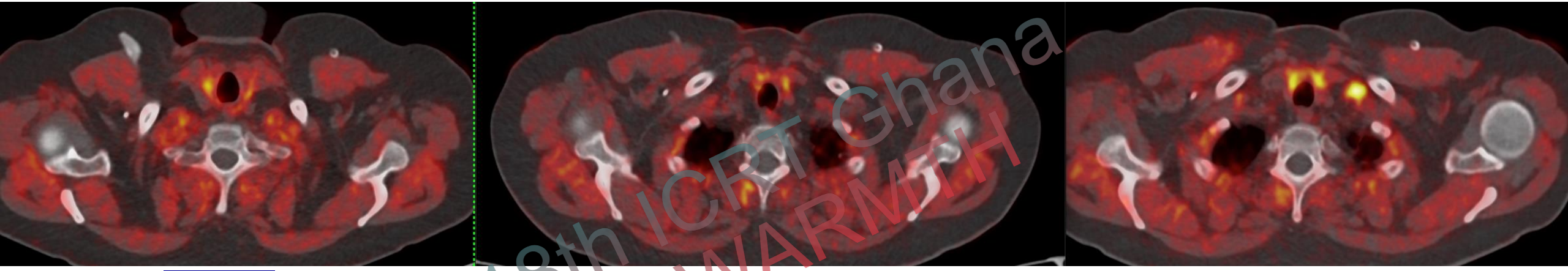
^{68}Ga-3BP-3940 FAP coronal images

Ovarian Cancer

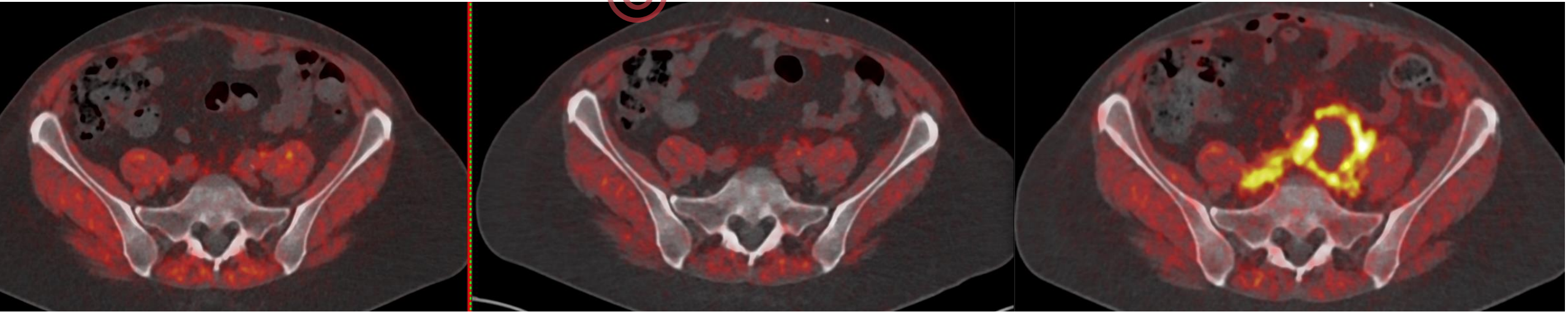
- retroclavicular and pelvic lymph node metastases -

baseline, and 9 and 12 months follow-up

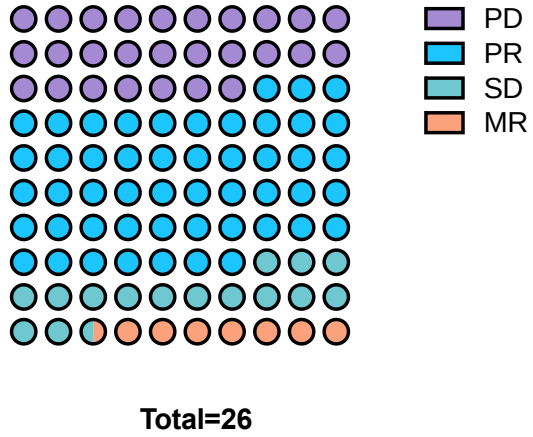
^{68}Ga-3BP-3940 FAP transversal images



Jan‘23 Oct‘22 FEB‘22



PTRT using 3BP-3940 – Tumor response



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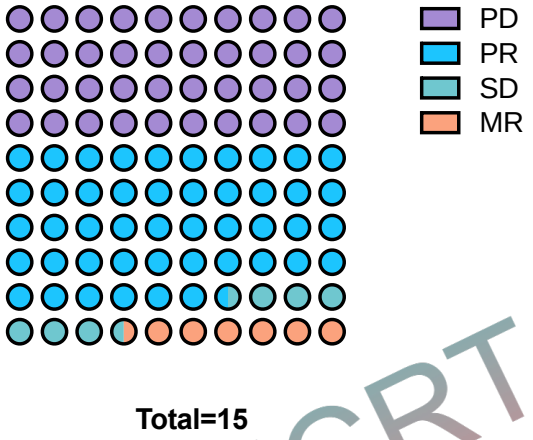

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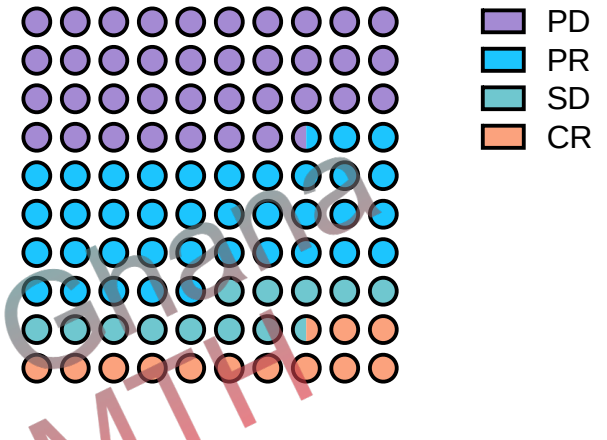

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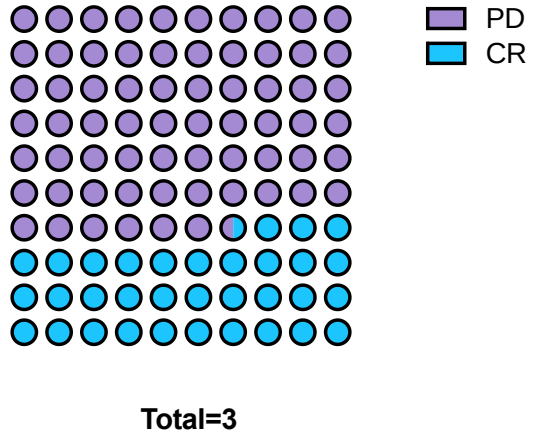

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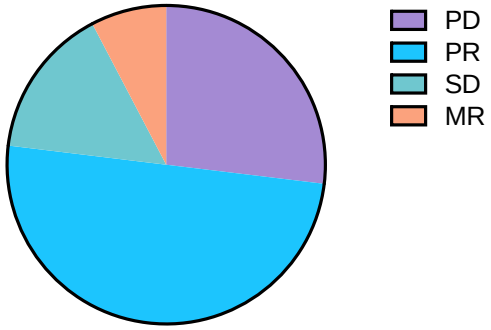

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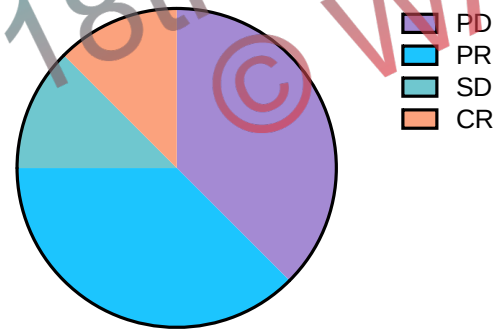

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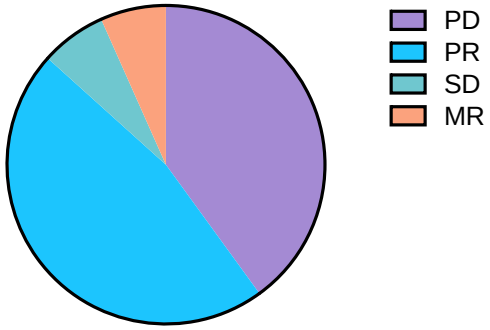

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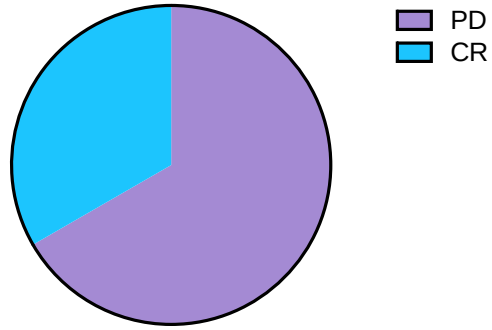

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Post Cycle 1

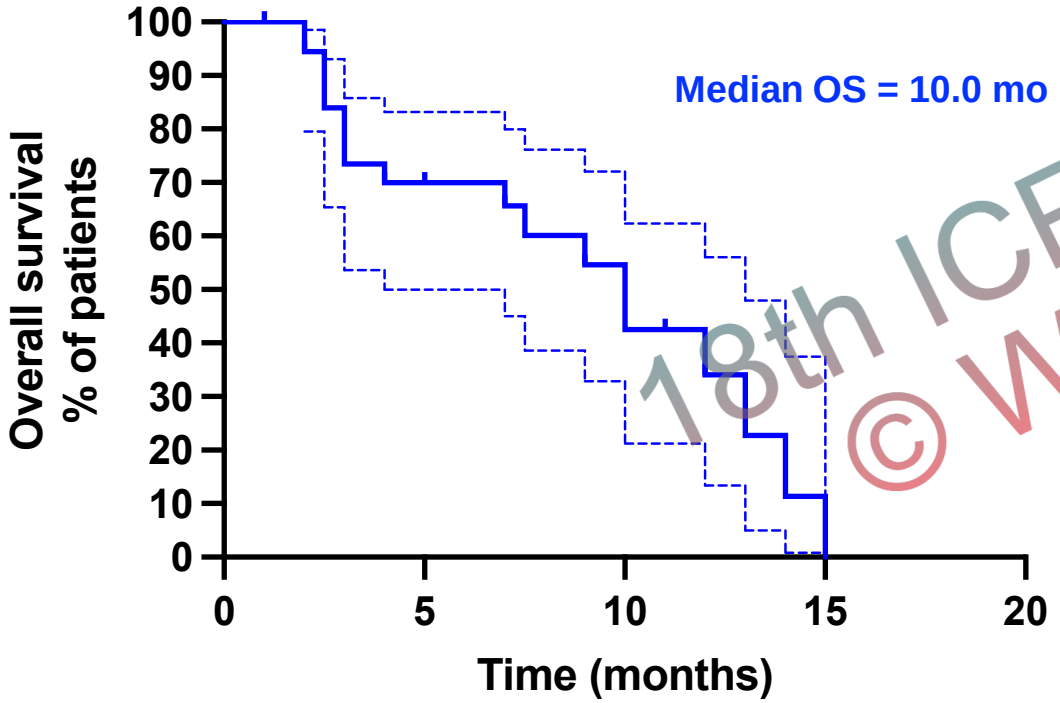
Post Cycle 2

Post Cycle 3

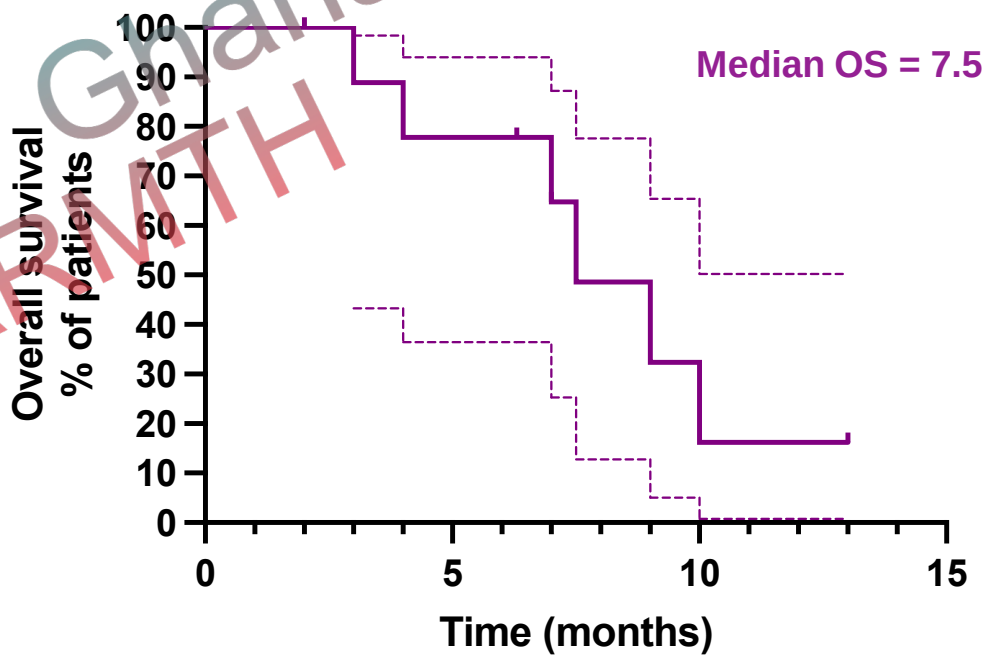
Post Cycle 4

Overall survival
from start of PTRT with ^{177}Lu / ^{90}Y / ^{225}Ac-3BP-3940

Overall survival (OS) for all patients (*n* = 40)

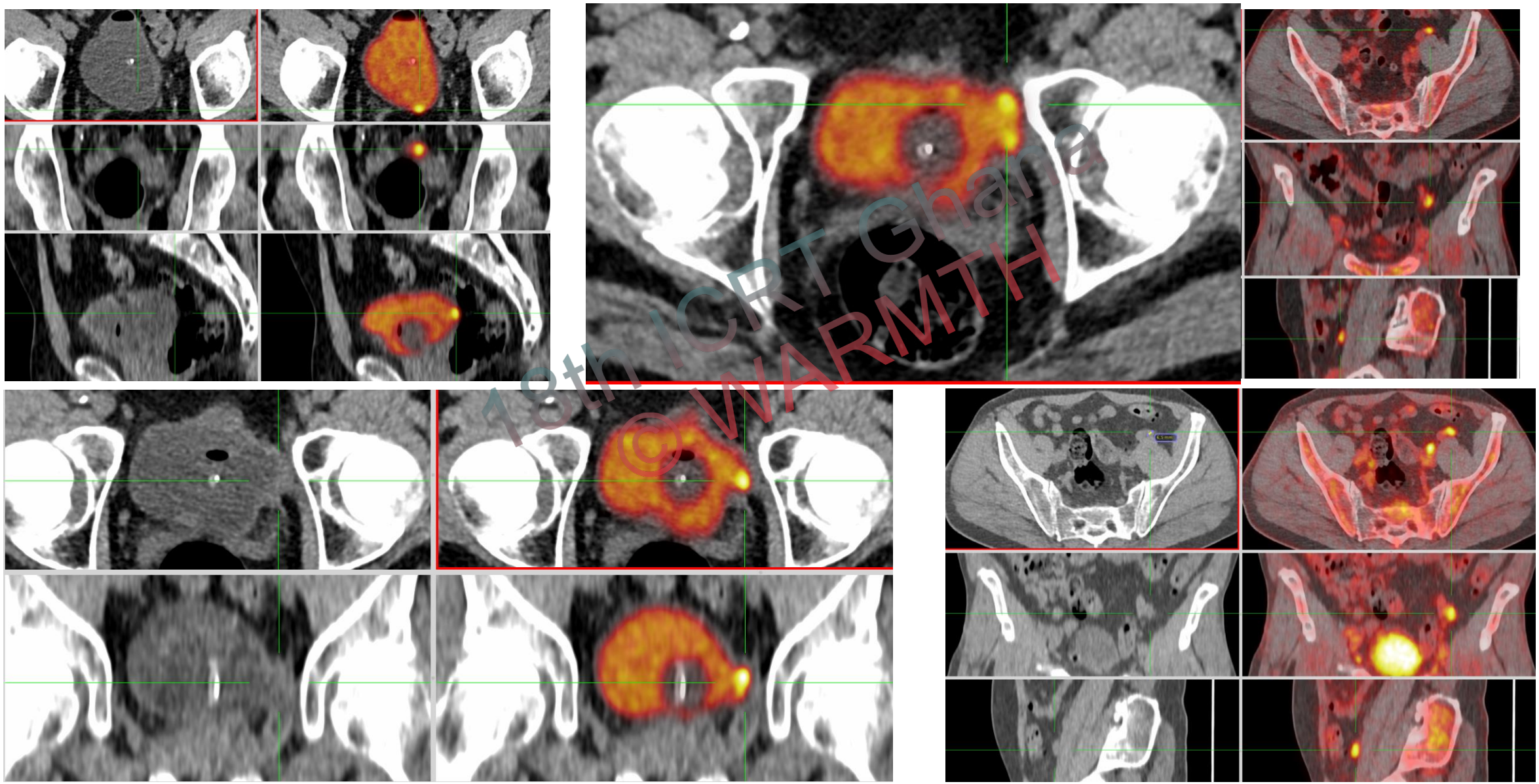


Overall survival (OS) for patients with pancreatic adenocarcinoma (n = 10)



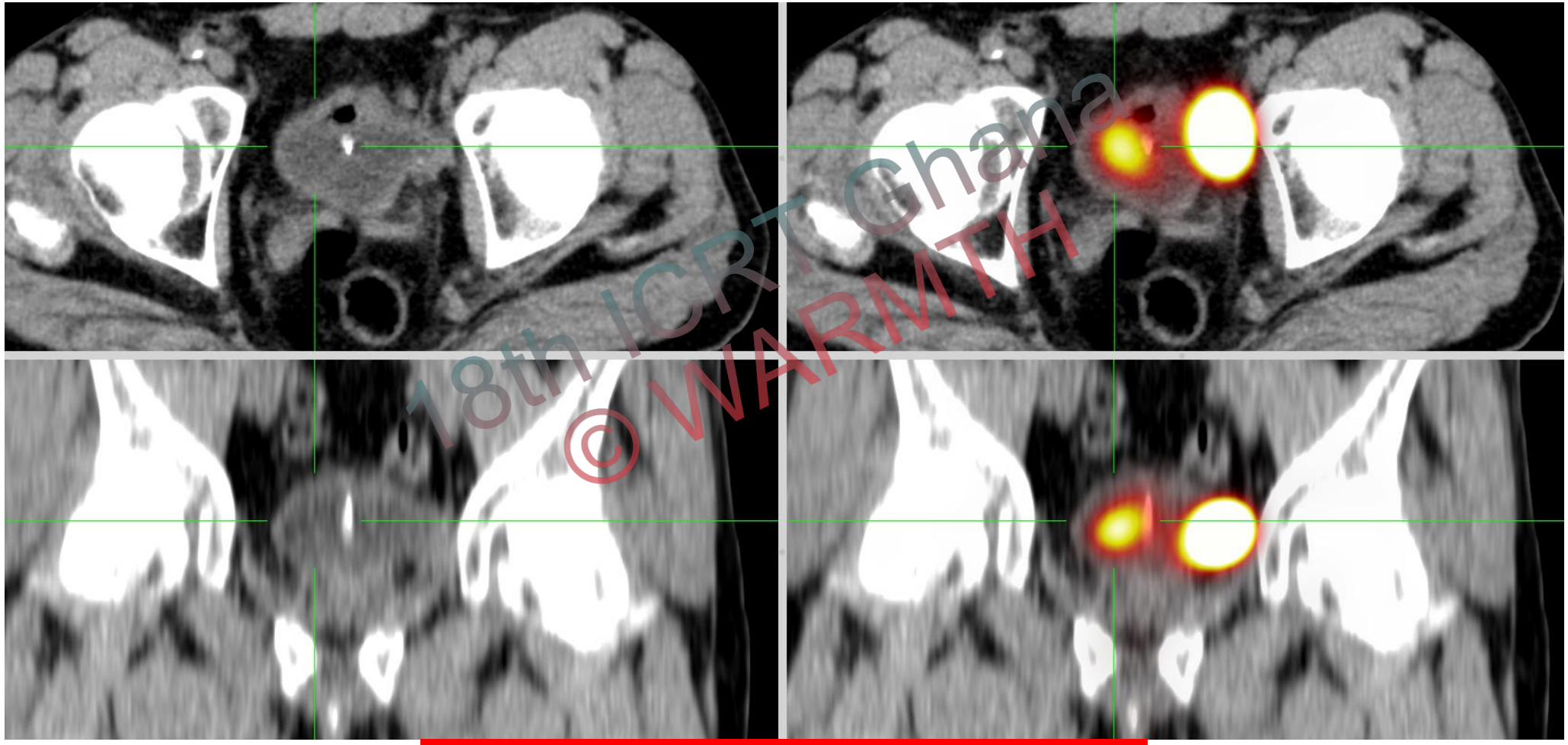
Kaplan-Meier curves for overall survival (OS) for all patients (n = 40) and the subgroup with pancreatic adenocarcinoma (n = 10) from start of ^{177}Lu/^{90}Y/^{225}Ac-FAP-3BP-3940 PTRT

Theranostics of Bladder Carcinoma („Incubator Concept“) using Ga-68 CXCR4 – First in human (March 2023)



Theranostics of Bladder Cancer („Incubator Concept“) using ^{177}Lu-3BP-3940 – First in human (March 2023)

^{177}Lu-FAP-3940 SPET/CT (16-Mar-2023)



New perspectives!!

ICPO Theranostics FAP Summit

Targeting the Tumor Microenvironment and Beyond

Friday 4 & Saturday 5 November 2022

VIRTUAL EVENT

www.icpo.foundation

See a world-class scientific program and invited representatives from academia and industry to dive deep into the topic of the Fibroblast Activation Protein (FAP), its history and role in biology of disease, current research and future applications.

https://www.icpo.academy/login.php?target=&client_id=icpo&auth_stat=

nature biotechnology

Elie Dolgin

Published: 06 December 2018

Radioactive drugs emerge from the shadows to storm the market

Novartis is expanding its push into radiotherapeutics. In October, the drug giant struck a $2.1 billion deal to acquire Endocyte, the maker of a late-stage candidate for prostate cancer that combines the tissue-killing power of radiation with a small molecule that binds preferentially to tumor cells. And less than a year ago, Novartis paid $3.9 billion to get hold of Lutathera (lutetium Lu 177 dotatate), a first-in-class peptide-based radionuclide therapy and the first approved by the US regulators, by acquiring the French company Advanced Accelerator Applications (AAA), based in Saint-Genis-Pouilly.

Experts in nuclear medicine see both these investments as validation for a therapeutic strategy that struggled for decades to move beyond radioactive iodine-131, a staple of thyroid cancer treatment since the 1940s. "It's been a long struggle," says Jim Ballinger, a nuclear medicine researcher at King's College London. "It's good to see that some products have been successful and taken on by big pharma."

Stem Jems / Science Source

Prostate cancer cells, the target of Endocyte's radioligand therapy, which attaches a radioactive atom to a small molecule designed to bind PSMA, a protein highly expressed on this type of cancer cell but absent on most healthy tissue.

FAP: The Next Billion Dollar Nuclear Theranostics Target?

Jeremie Calais[1]– THE JOURNAL OF NUCLEAR MEDICINE • Vol. 61 • No. 2 • February 2020

[1]Ahmanson Translational Theranostics Division, Department of Molecular & Medical Pharmacology, University of California Los Angeles, Los Angeles, California; [2]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, California; [3]Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; and [4]Institute of Urologic Oncology, University of California Los Angeles, Los Angeles, California

The growth of Theranostics is transforming approaches in treating cancer. AuntMinnie.com - November 5th, 2022

With radiotherapeutics representing 21% of the total radiopharmaceutical market today (with a forecast of 74% by 2031) and 100+ companies with products under development looking to enter nuclear medicine/radiotherapeutics[1], it seems the growth will only continue.

Clovis Oncology falls 55% on bankruptcy concerns November 9th, 2022

Nov. 09, 2022 8:45 AM ET | **Clovis Oncology, Inc. (CLVS)** | By: Dulan Lokuwithana, SA News Editor | 12 Comments

NOVARTIS

3B Pharmaceuticals

PRESS RELEASE

3B Pharmaceuticals enters into a Global Exclusive Licensing Agreement for its FAP-Targeting Peptide Technology

Licensing agreement includes exclusive worldwide rights to develop and commercialize therapeutic and imaging applications for 3BP's FAP-targeting technology; 3BP retains certain rights to develop FAP-targeted imaging agents

Berlin, April 24, 2023 – 3B Pharmaceuticals GmbH (3BP), a private German biotechnology company developing targeted radiopharmaceutical drugs and diagnostics for oncology indications, today announced that it has entered into an amended and restated licensing agreement with Novartis Innovative Therapies AG (Novartis) for 3BP's FAP-targeting peptide technology.

Acknowledgements - National and international collaborators over the years

The CURANOSTICUM Team

- **Lukas Greifenstein**
- **Aditi Mishra**
- **Alexandr Eismant**
- André Klega
- Corinna Müller
- Christian Landvogt
- Daniel Benz-Zils

Radiochemistry

- Helmut Mäcke, Basel/Freiburg
- Frank Rösch, Mainz
- Hans-Jürgen Wester, Munich
- Thea Maina-Nock, Athens
- Jae Min Jeong, Seoul
- Michael Schultz, Iowa
- Cristina Müller, Villigen (PSI Team)
- Andreas Türler, Berne

Medical Physics

- Thomas Beyer, Vienna

Molecular Pathology

- Ralph Wirtz, Cologne
- Jean-Claude Reubi, Berne
- Stefan Schulz, Jena

Scientists / Physicians

- Richard Wahl, St. Louis (prev. Ann Arbor and Baltimore)
- Steve Larson, New York
- Jean-Francois Chatal, Nantes
- Lisa Bodei, Milano / New York
- Eric Krenning, Marion de Jong, Rotterdam
- Irvin Modlin, Yale University
- Marianne Pavel, Erlangen
- Patricia Grabowski, Berlin
- **Jingjing Zhang, Singapore**
- Elcin Zan, New York
- Andrea Frilling, London
- Jeremie Calais, Los Angeles
- Martin Pomper, Johns Hopkins Baltimore,
- Oliver Sartor, Tulane University, New Orleans
- Michael Morris, MSKCC, New York
- Christiane Smerling, Berlin
- Anthony Chang/Anderson Peck, Grand Rapids
- Baljinder Singh, Chandigarh
- Feng Wang, Nanjing
- Philippe Lambin, Maastricht
- Andrew Schally, Miami
- Gerd Binnig, Munich

- Zentralklinik Bad Berka (1997-2019)
- Harshard R. Kulkarni
- Aviral Singh
- Christiane Schuchardt

ICPO Foundation, Wiesbaden
Dinse Foundation, Hamburg
All patients (esp. Josh Mailman)
and many others..

7th THERANOSTICS WORLD CONGRES MARCH 22-24, 2024 SANTIAGO, CHILE

- Prostate Cancer
- Neuroendocrine Tumors
- Targeting the Tumor Microenvironment
- New Radioisotopes and their Production
- Novel Radiochemistry and Chelators
- Combination Therapies
- Patients' Access and many other topics

Thank you for your attention!

www.twc-2024.org