THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Homer A. Macapinlac, M.D.

Ajit Padhy Oration: The Key is Theragnostics.

Cancer Statistics, 2023

Estimated New Cases

			Males	Females			
Prostate	288,300	29%			Breast	297,790	31%
Lung & bronchus	117,550	12%			Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%			Colon & rectum	71,160	8%
Urinary bladder	62,420	6%			Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%			Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%			Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%			Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%			Pancreas	30,920	3%
Leukemia	35,670	4%			Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%			Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**			**All Sites**	**948,000**	**100%**

Estimated Deaths

			Males	Females			
Lung & bronchus	67,160	21%			Lung & bronchus	59,910	21%
Prostate	34,700	11%			Breast	43,170	15%
Colon & rectum	28,470	9%			Colon & rectum	24,080	8%
Pancreas	26,620	8%			Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%			Ovary	13,270	5%
Leukemia	13,900	4%			Uterine corpus	13,030	5%
Esophagus	12,920	4%			Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%			Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%			Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%			Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**			**All Sites**	**287,740**	**100%**

CA A Cancer J Clinicians, Volume: 73, Issue: 1, Pages: 17-48, First published: 12 January 2023, DOI: (10.3322/caac.21763)

- 2nd most common cause of death
- Progress: Reduction of Mortality rate to 143.8/100,000
- Decline of 33% since 1991
- Smoking reduction
- Improved Rx of lung, CRC, breast and prostate cancer
- Prostate CA 29% of diagnosis
- Women: breast, lung, CRC 51%
- No accounting for disruption of health services due to COVID

Evolution of NM practice

- Multimodality imaging
  - PET/CT digital/LFOV: sensitivity/accuracy
  - SPECT/MDCT: pre/post therapy assessments
- Adjuvant therapy aimed at improving PFS or OS.
  - NET's, prostate cancer, metastases to bone, liver etc
- Ambulatory Tx Centers: Faculty and clinical support.
  - Clinical trial experience – optimize FDA approved therapy.
- Integration in guidelines for combinatorial/sequential Rx

Integration into Multi-Disciplinary Care Team

- Surgical Oncology, Medical Oncology, Radiation Oncology, Molecular Pathology
  - Radiology/Nuclear Medicine (multimodality/theragnostic).

- Focused Clinical Trial/Therapy for Patient.
  - Radionuclide based therapy*
  - NM primary: patient selection, combination therapy

Theragnostics
Diagnose and Treat Cancer

Tumor	Target	Diagnostic	Therapeutic
Thyroid Ca	NaI Symporter	I-123/I-131/I-124 NaI	I-131
Prostate Ca	Hydroxyapatite	Tc-99m MDP/NaF	Ra-223
	PSMA	Ga-68/F-18 PSMA	Lu-177/Ac-225*
Neuroendocrine	Somatostatin Receptor	Ga-68/Cu-64 DOTATATE	Lu-177/Ac-225*
Paraganglioma Neuroblastoma	Norepinephrine transporter	I-123 MIBG (HSA)	I-131
Hepatic	HCC**/CRC mets	Tc-99mMAA/angiography	Y-90 therasphere/sirsphere

Teyateeti, A. et.al. World J Gastroenterol. 2021 Dec 21;27(47)**

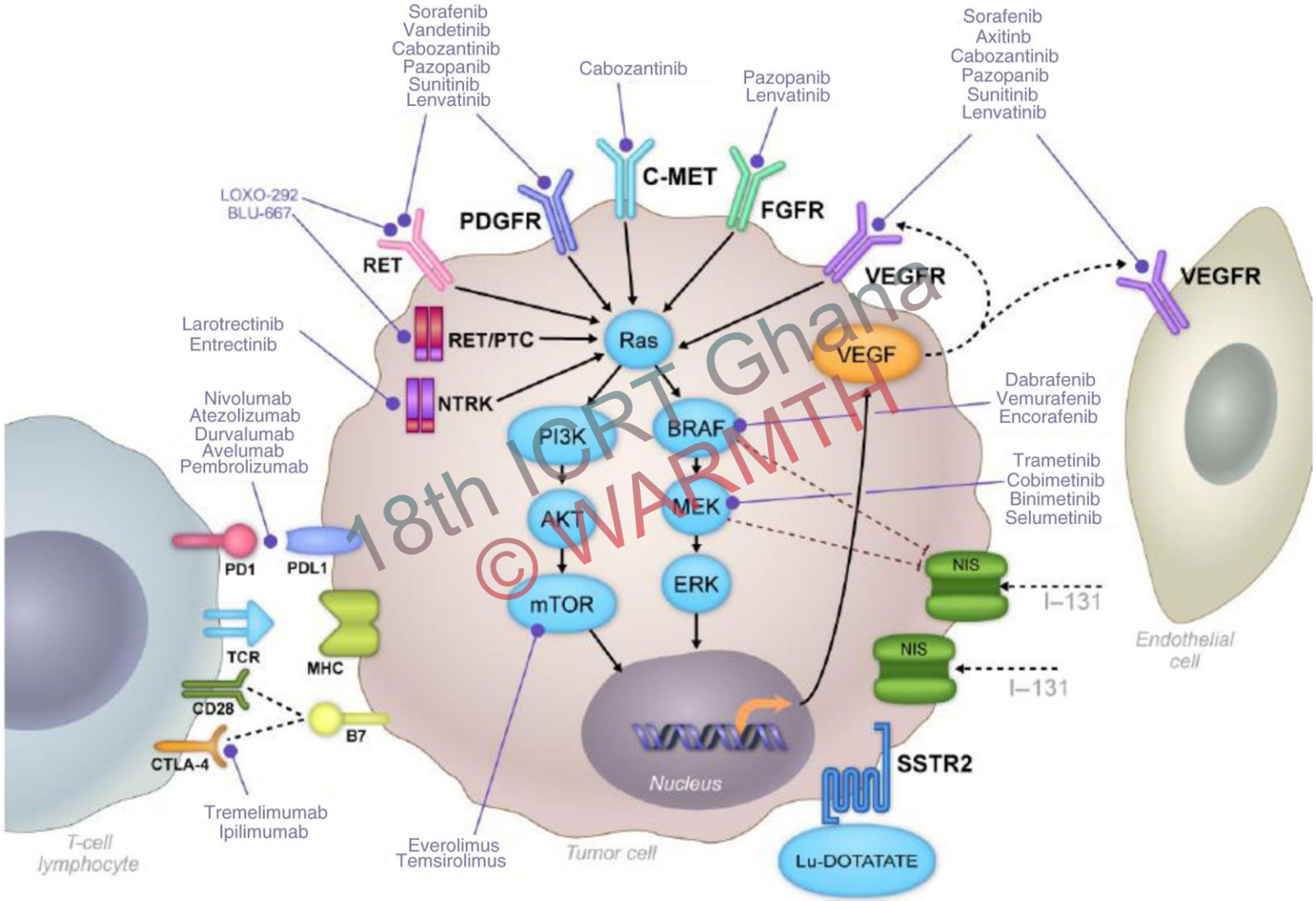
*Clinical Trials, not yet FDA approved

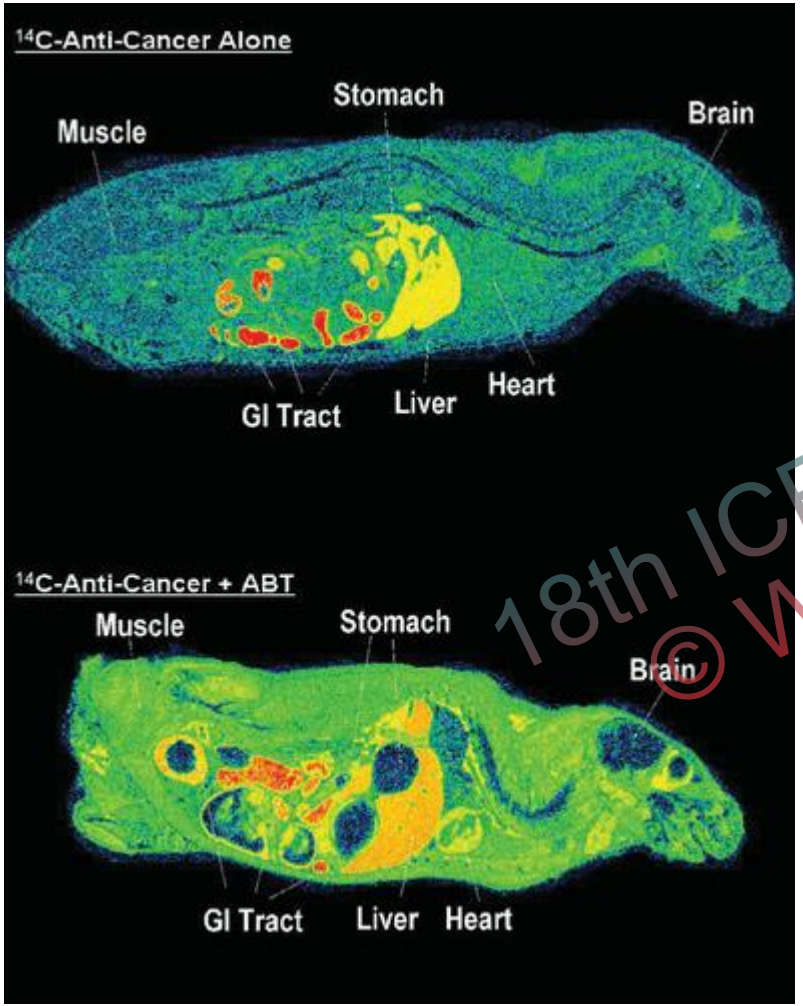
Differentiated Thyroid Ca

- 90%, increasing incidence, excellent survival
- Therapy: Consensus Guidelines
  - Total thyroidectomy, I-131 (high risk, adjuvant Rx)
  - Local recurrence treated with I-131, surgery, XRT
  - Distant metastases – 30% CR with I-131
- RAI resistant: FDG avid, I-131 (-), CT/MR (+)
  - Sorafenib, Lenvatinib, Vandetanib, Cabozantinib
    - Impressive PFS improvement but not OS
  - BRAF-mutated anaplastic carcinoma
    - dabrafenib/trametinib combination yielded a 69% objective response rate, with 90% of responses lasting at least 12 months and a 12-month OS of 90%

Haugen, BR and Sherman, SI. Endocrine Reviews 34: 439–455, 2013

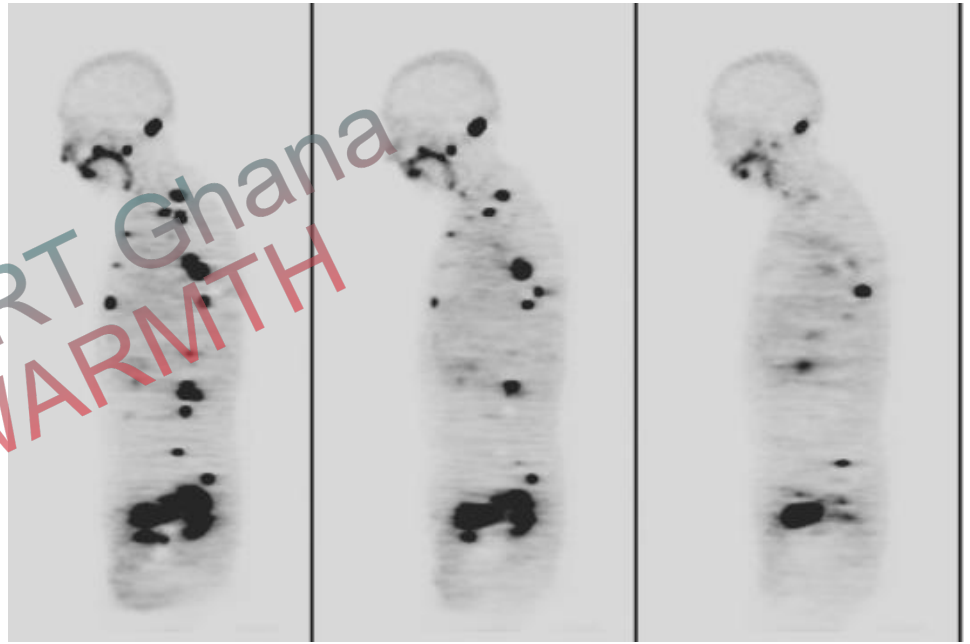
Sherman, SI Evolution of Targeted Therapies Thyroid Carcinoma. Trans Am Clin Climatol Assoc. 2019;130:255-265.





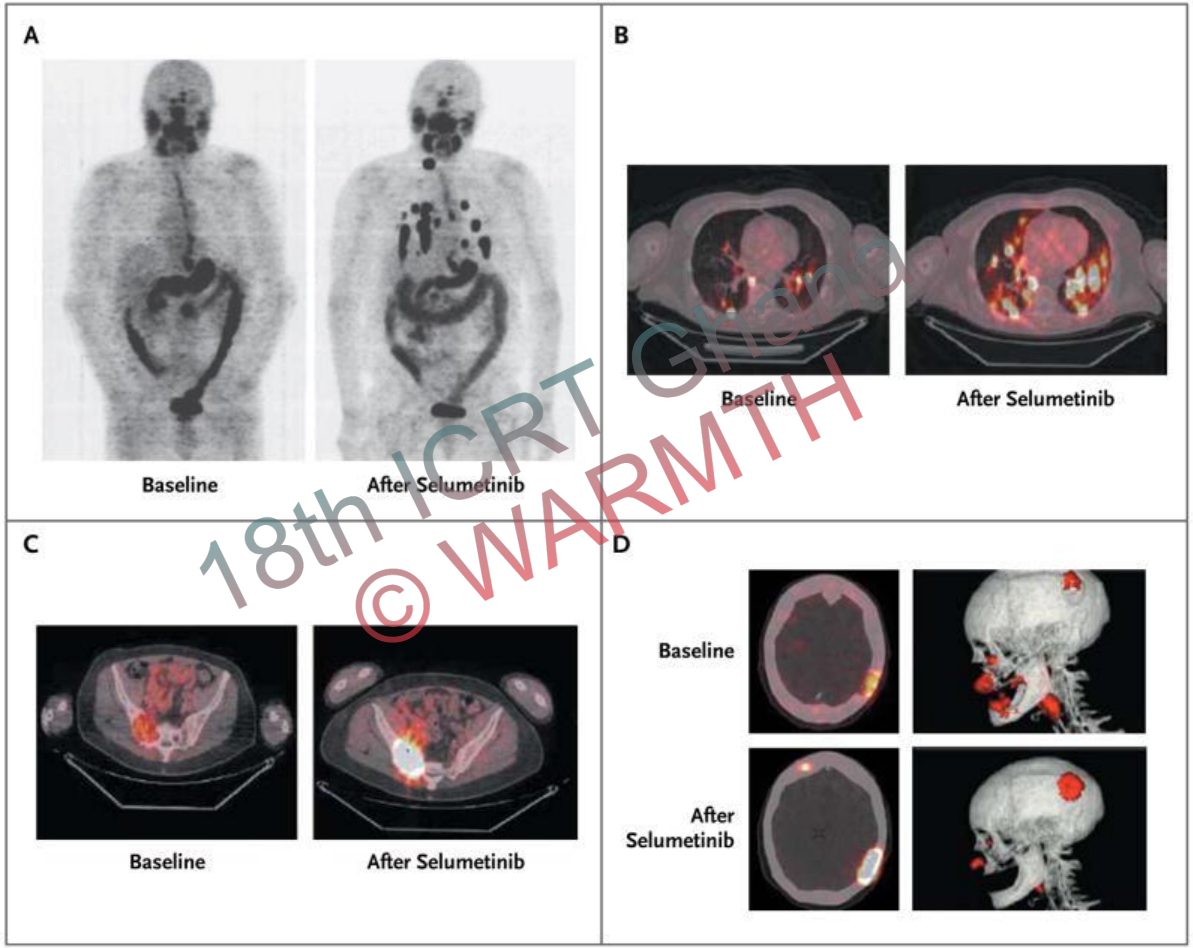
Chem Res Toxicol. 2012 Mar 19;25(3):543-55

Radiation Dose Assessment for I-131 Therapy of Thyroid Cancer Using I-124 PET

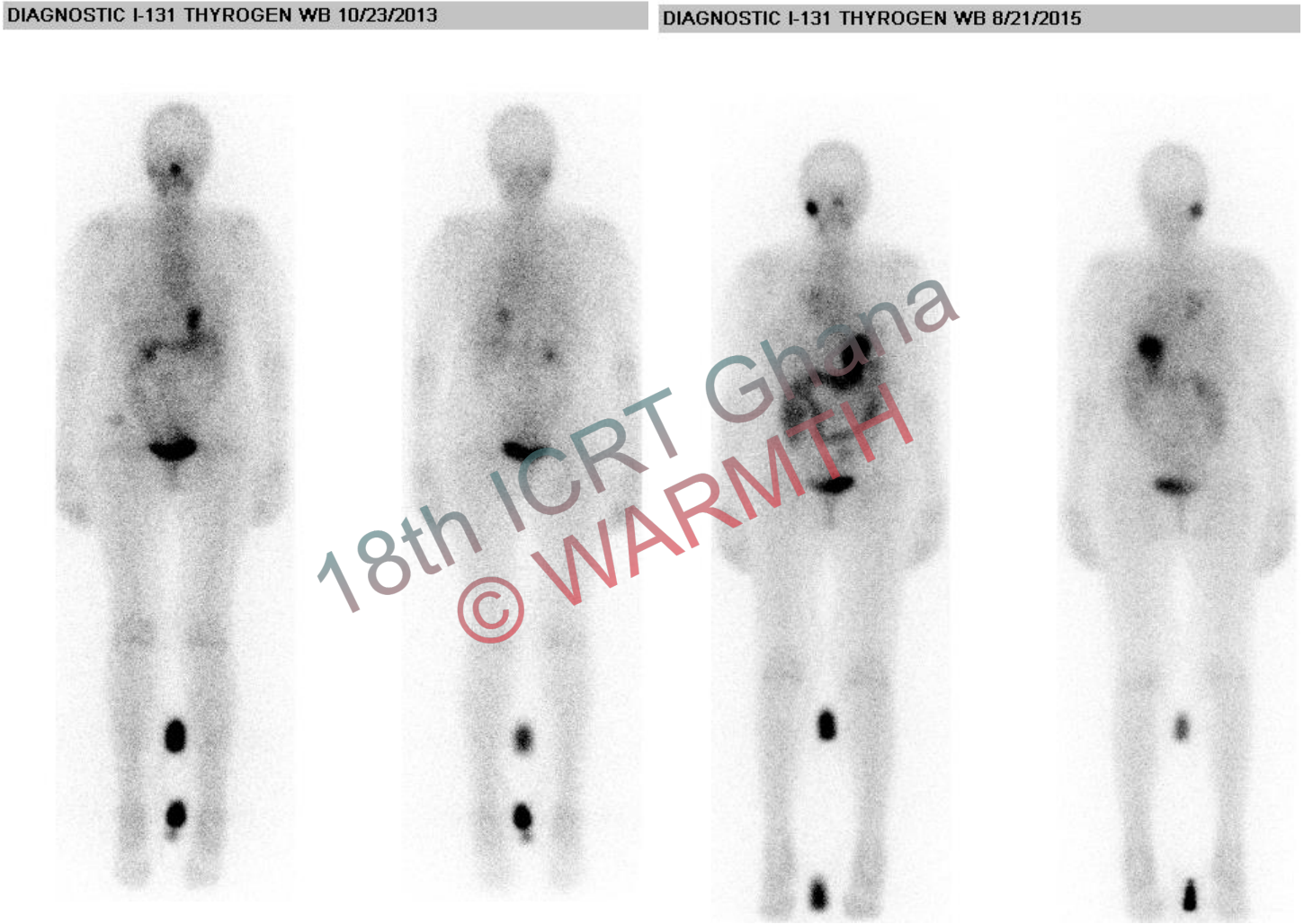


Clin Positron Imaging. 1999 Jan;2(1):41-46.

Iodine-124 PET-CT before and after Selumetinib Treatment

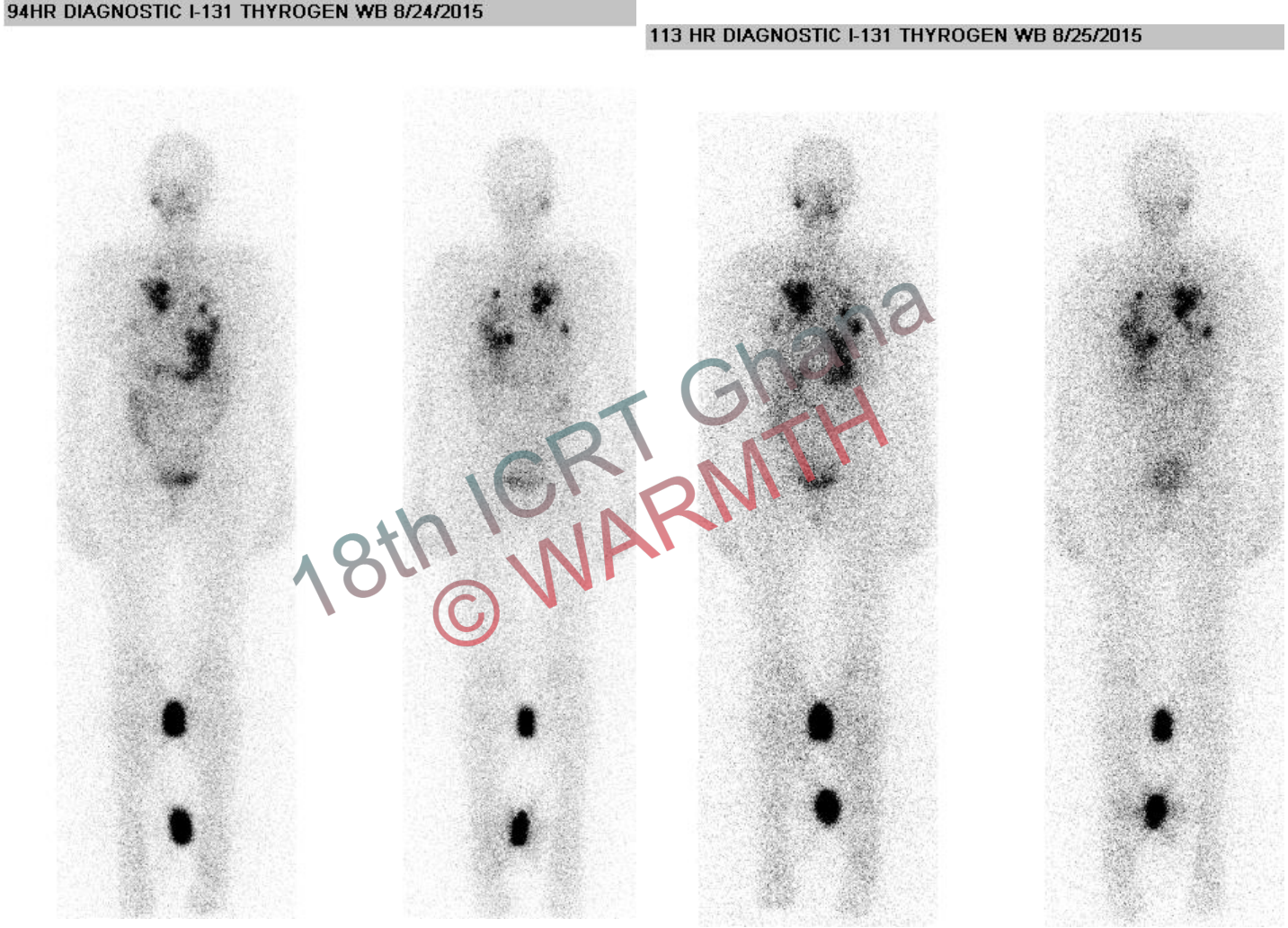


N Engl J Med. 2013 Feb 14;368(7):623-32.



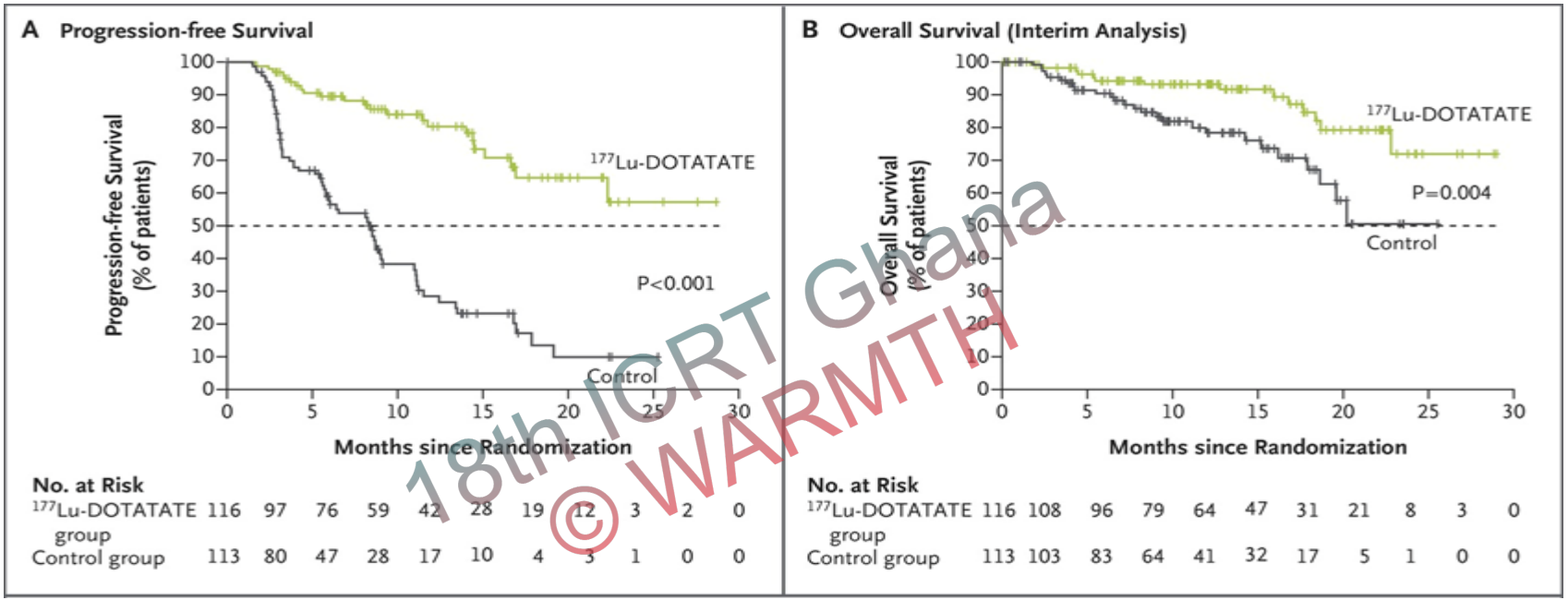
72 year old with follicular thyroid ca KRAS mutated

MEK16 inhibitor 45mg BID



Post therapy Scan after 208 mCi of I-131 NaI

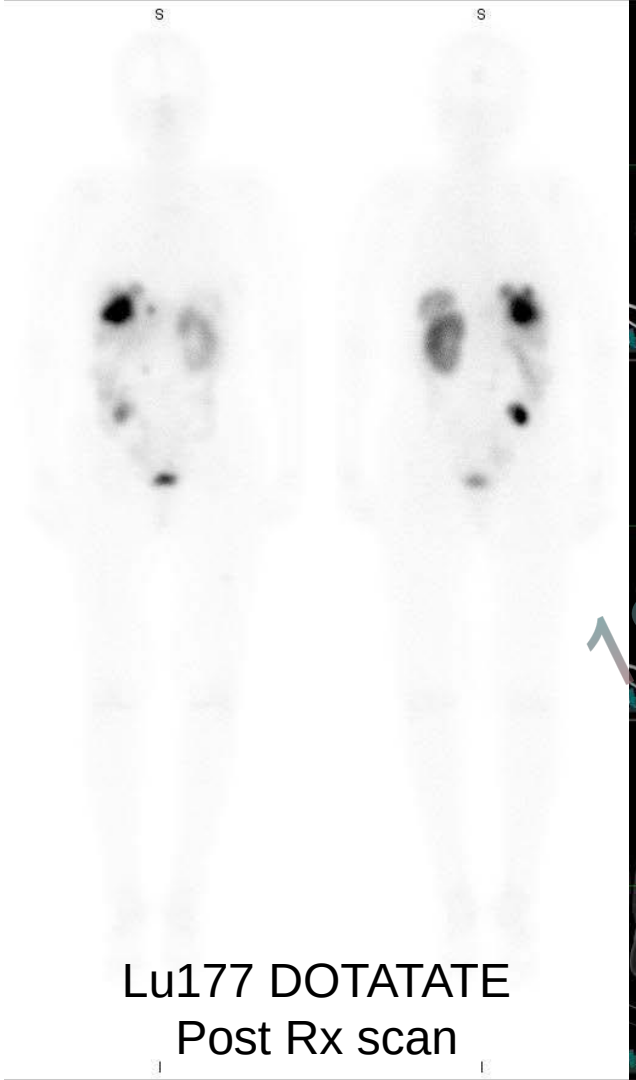
Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors



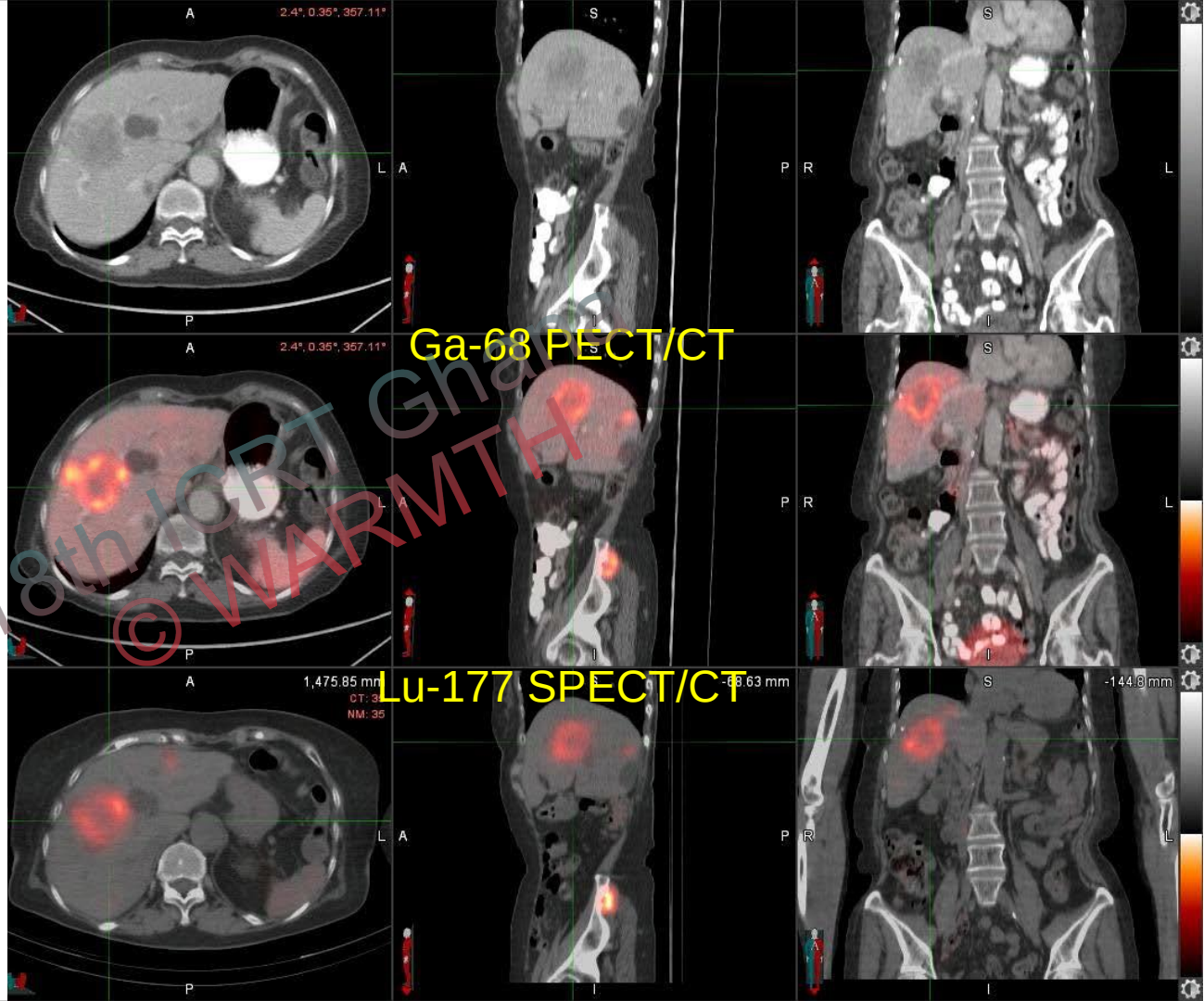
Treatment with 177Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors.

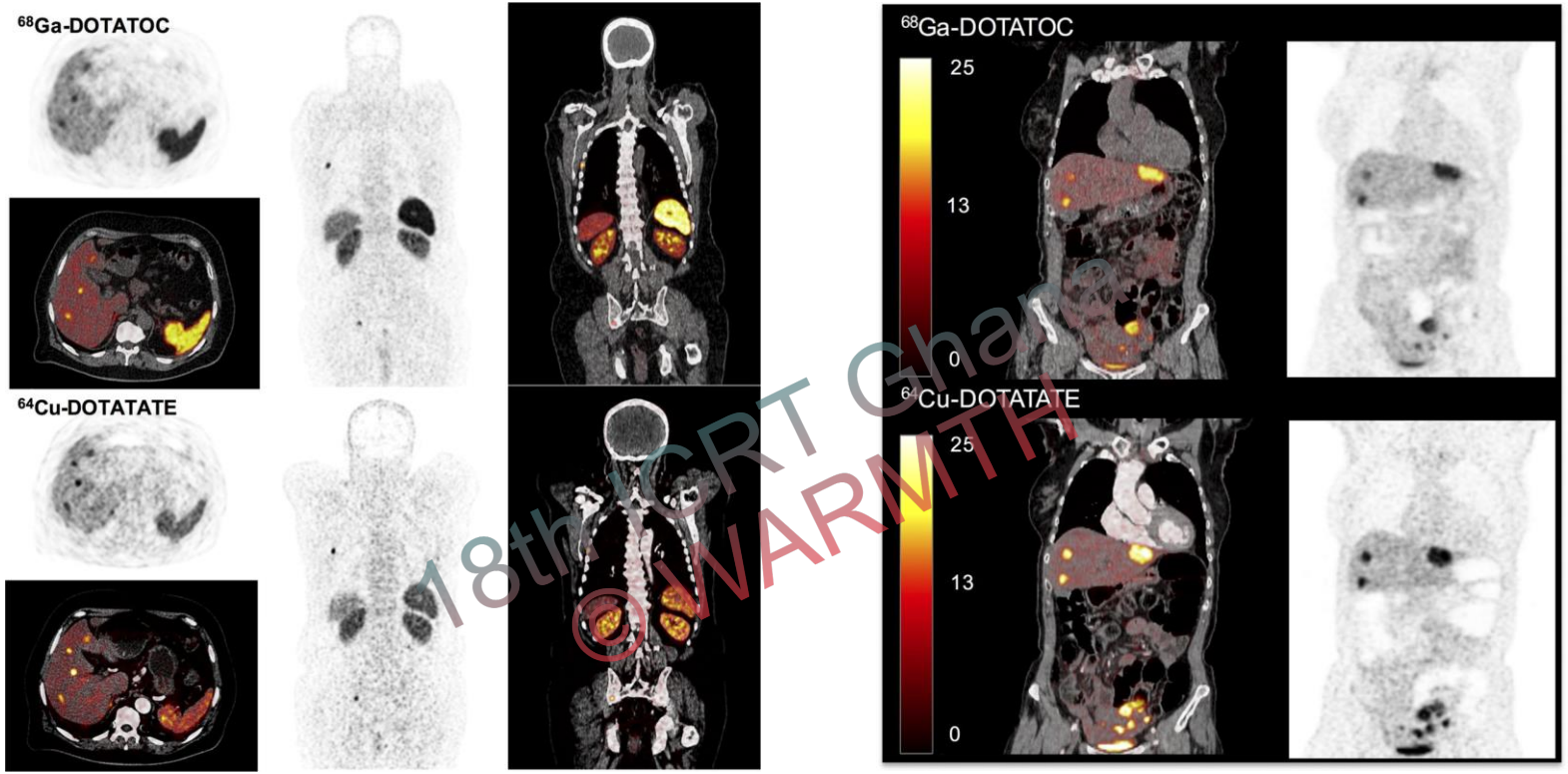
N Engl J Med 2017; 376:125-135 January 12, 2017

The NEW ENGLAND JOURNAL of MEDICINE



Lu177 DOTATATE
Post Rx scan





68Ga- and 64Cu-DOTATATE PET/CT scans (color) and PET scans (black and white) of patient with intestinal NET and multiple metastases. Camilla B. Johnbeck et al. J Nucl Med 2017;58:451-457

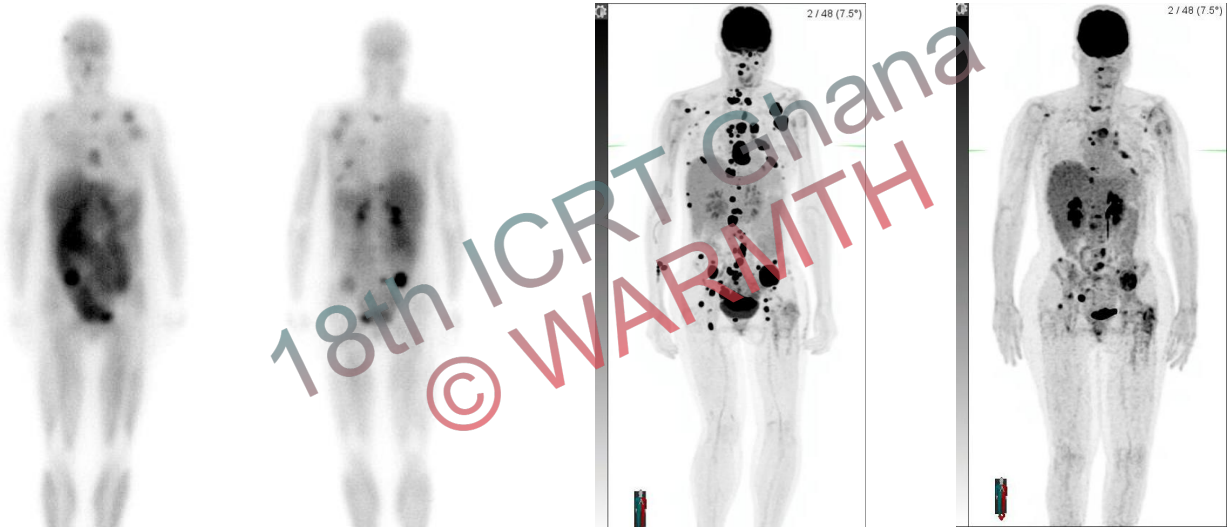
High Specific Activity I-131 MIBG

- Screen for meds which <catecholamine uptake
- Dosimetry 3 visits
  - Infusion, WB scans on days 1-2 and days 2-5
  - 8 mCi/kg (up to 500 mCi)
  - lung, liver, and kidney doses that would not exceed 17.5 Gy, 30 Gy, and 23 Gy.
- Inpatient Rx (7-14 days)

- Premedication for N/V
- platelet > 80,000 µL and (ANC) 1200 µL
- 2nd Rx 90 days
  - Dose reduction if platelet < 25,000 µL and (ANC) 500 µL,febrile neutropenia, Hb<6.5g/dl

Jimenez C, et.al. Targeted Radionuclide Therapy for Patients with Metastatic Pheochromocytoma and Paraganglioma: From Low-Specific-Activity to High-Specific-Activity Iodine-131 Metaiodobenzylguanidine. Cancers, 2019 Jul 20,

34 year old female with metastatic paraganglioma post therapy including 1 Curie of I-131 MIBG HSA



I-131 MIBG Post therapy scan FDG PET/CT pre post therapy scans

>25 years of PRRT

- Approved for Neuroendocrine tumors Therapy
- Efficacy and tolerability
- Future directions
  - neuroblastoma
  - Limited disease and early therapy
  - Intra arterial, alpha Rx, new peptides, liquid bx

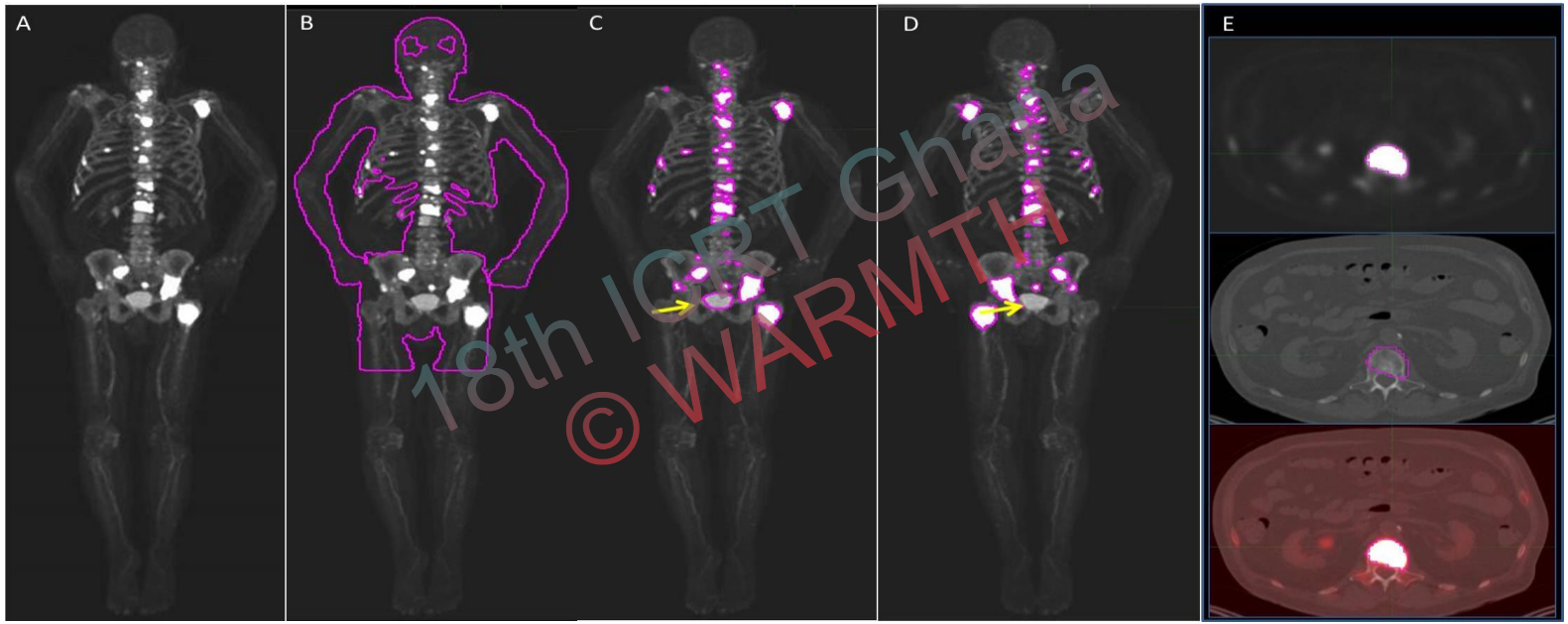
Bone Seeking Radionuclides
Mechanism of uptake

- Calcium analogues
  - Sr-89 Cl*
  - Ra-223 dichloride*
- Attached to phosphate
  - Sm-153 EDTMP*
  - Rh-186/188 HEDP
  - Lu-177 EDTMP
  - Sn-117^{m}DTPA
  - P-32

*approved agents

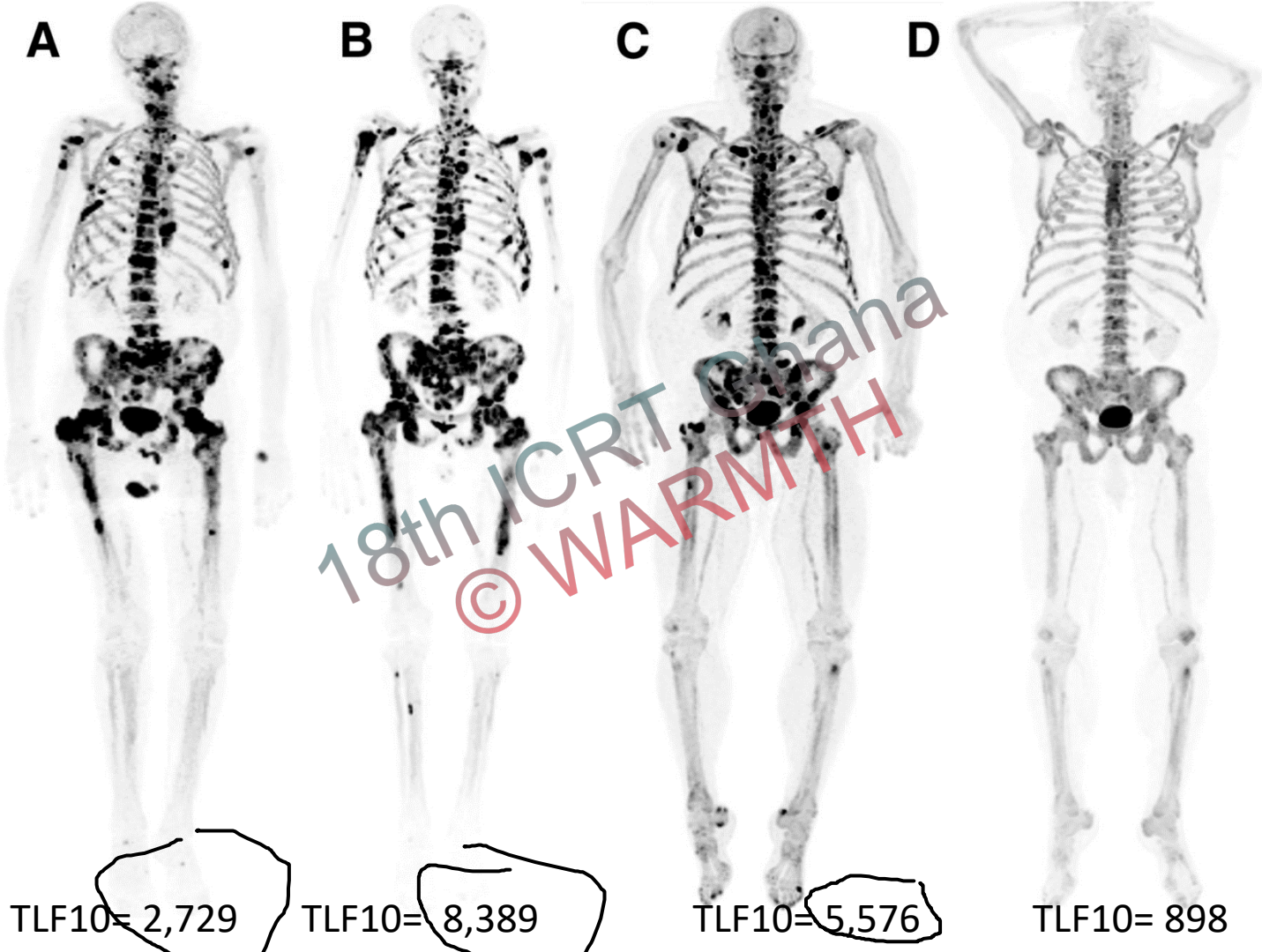
MDP Bone Scan NaF PET Scan

Skeletal Tumor Burden Assessment with Fluoride PET/CT

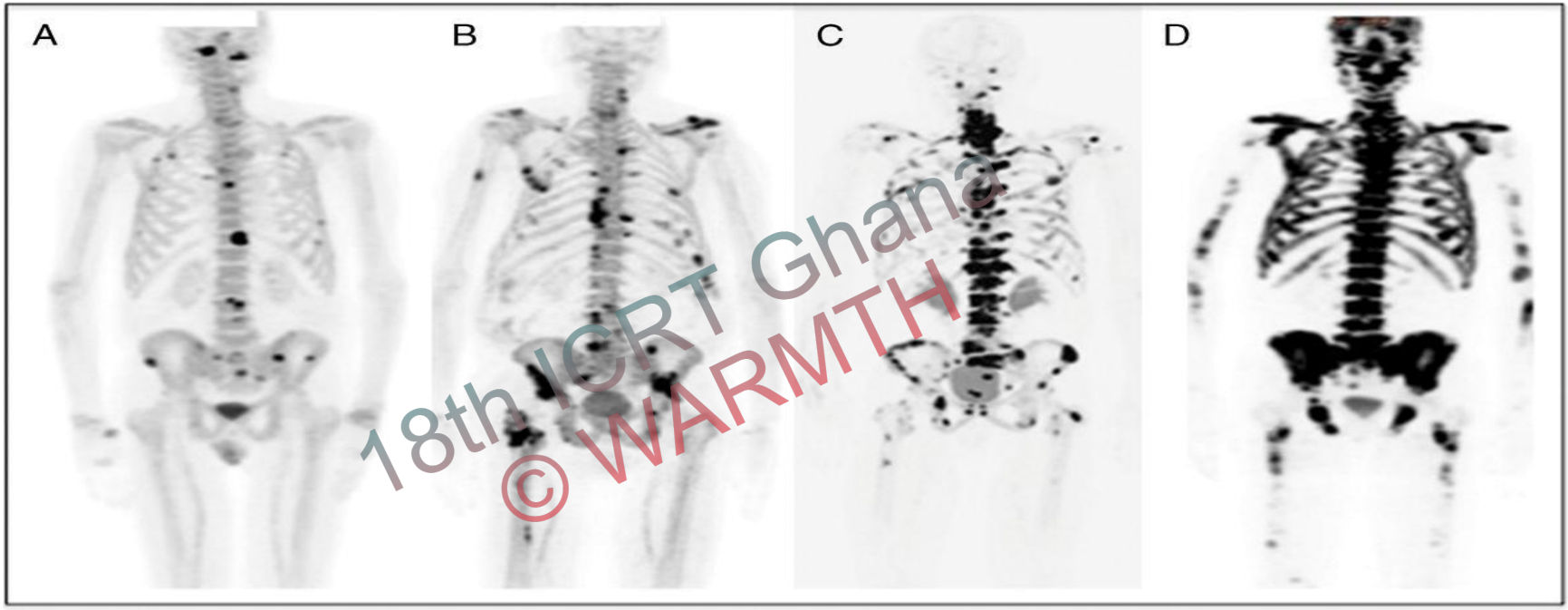


Fluoride PET/CT | semi-automatic VOI | BKG subtracted | Non met VOI subtracted

Etchebehere, et. al. J Nucl Med. 2015 Jun 11. pii: jnumed.115.158626. [Epub ahead of print]



18F-PET/CT Predicts Bone Marrow Failure After 223Ra Therapy.



Patients A and B were still alive and did not develop BMF. Patients C and D deceased. C, TLF10 = 8768 and FTV10 = 440, died without developing BMF. D, TLF10 = 25841 and FTV10 = 1569, died with BMF.

Etchebehere EC, et.al. Clin Nucl Med. 2016 Apr;41(4):268-73.

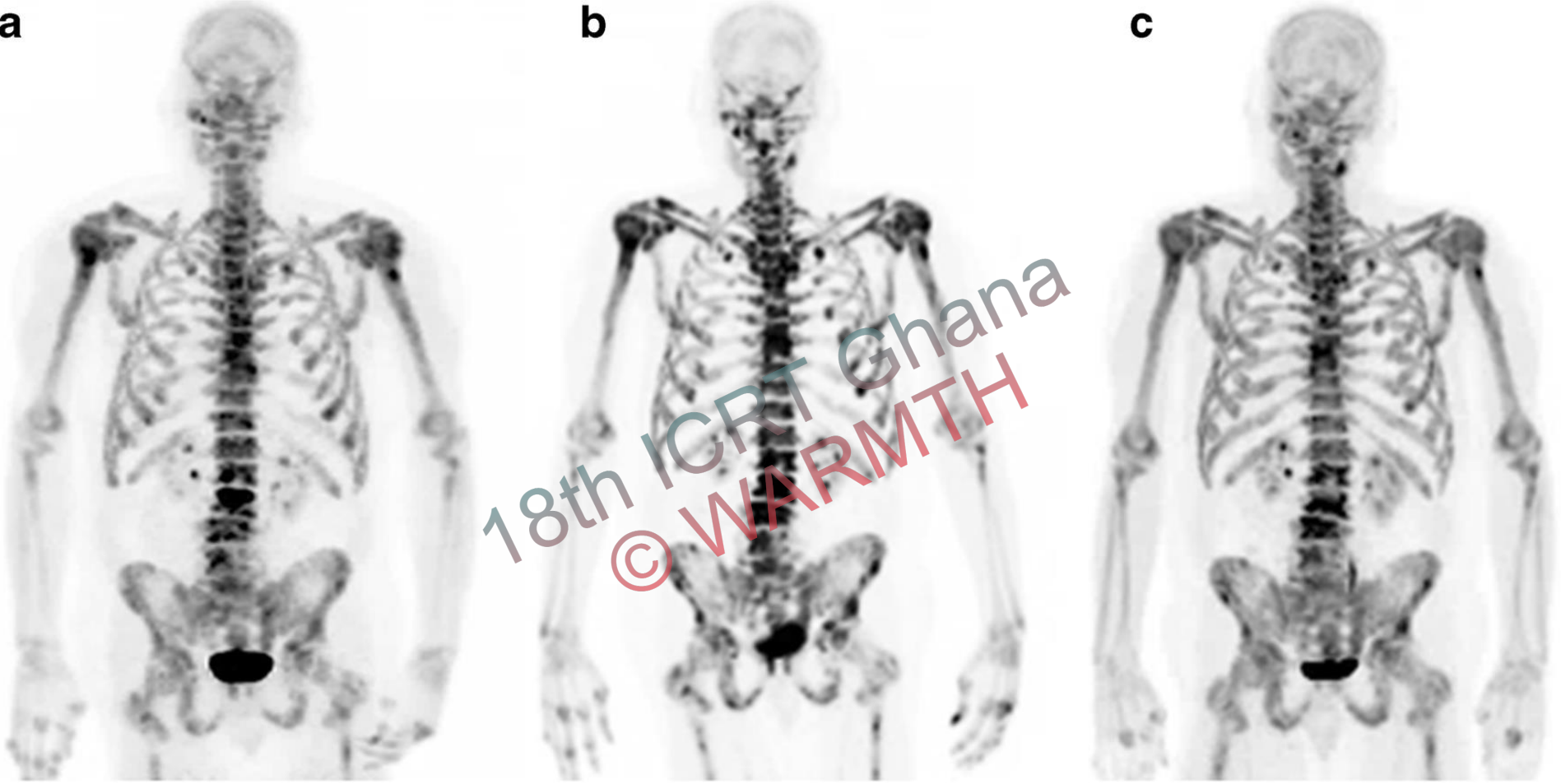
Prostate-specific antigen flare induced by 223RaCl2 in patients with metastatic castration-resistant prostate cancer.

- 168 patients with mCRPC (median age 69; median PSA 29.7) receiving 223RaCl2.
- OS and PFS, evaluated for patient groups corresponding to definitions of PSA flare

- well-known phenomenon during therapy with LHRH agonists and docetaxel- or cabazitaxel-based chemotherapy

- better OS and PFS in mCRPC patients experiencing PSA flare in 233RaCl2 therapy than those with progressive PSA increase, most of whom were already treated with androgen deprivation therapy, cytotoxic chemotherapy, hormone therapy, and palliative radiotherapy.

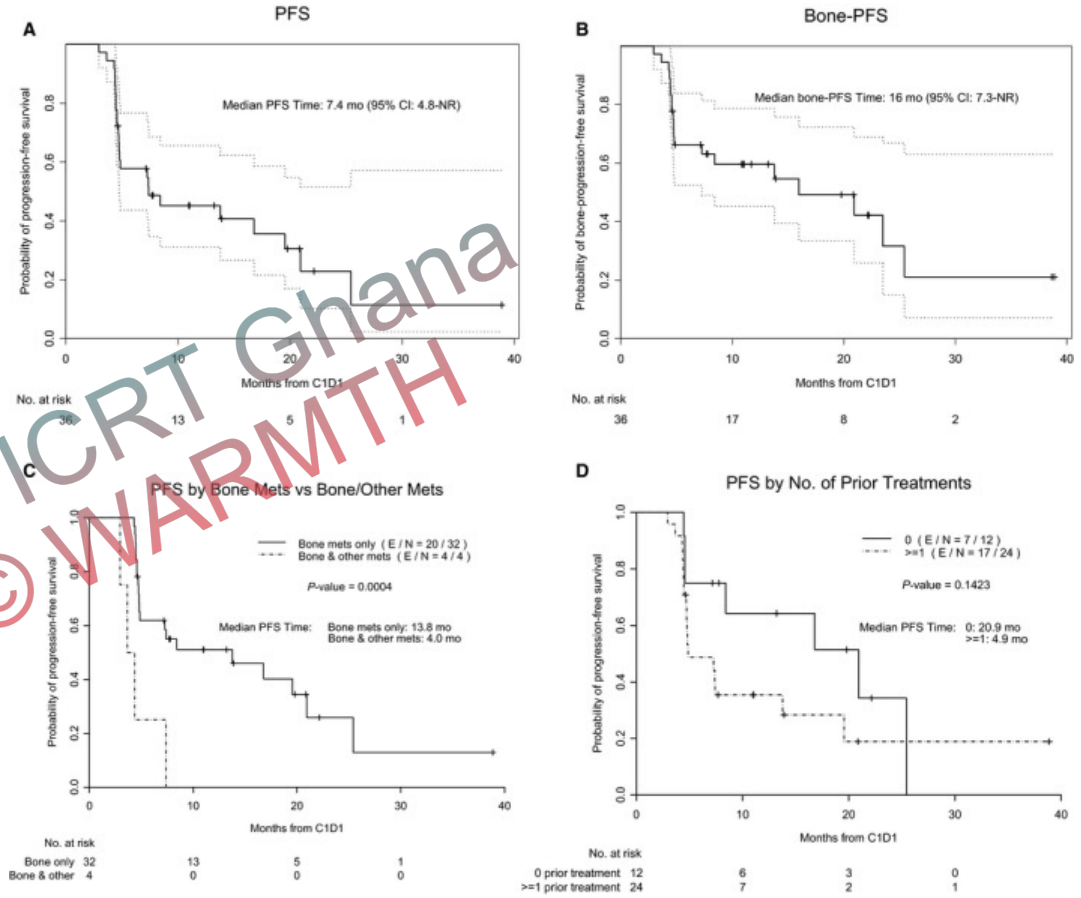
Eur J Nucl Med Mol Imaging. 2018 May 21. doi: 10.1007/s00259-018-4051-y. [Epub ahead of print]



Eur J Nucl Med Mol Imaging. 2018 May 21. doi: 10.1007/s00259-018-4051-y. [Epub ahead of print]

Phase II study of Ra-223 dichloride combined with hormonal therapy for hormone receptor-positive, bone-dominant metastatic breast cancer

- Single-center phase II study, 36 patients received Ra-223 (55 kBq/kg intravenously every 4 weeks) up to 6 cycles with endocrine therapy.
- The disease control rate at 9 months was 49%. The tumor response rate at 6 months was 54% (CR, 21%; PR, 32%). The median PFS was 7.4 months (95% CI, 4.8-not reached [NR]). The median bone-PFS was 16 months (95% CI, 7.3-NR). There were no grade 3/4 adverse events.
- Ra-223 with hormonal therapy showed possible efficacy in HR+ bone-dominant breast cancer metastasis, and adverse events were tolerable.



Cancer Med. 2020 Feb; 9(3): 1025–1032.

Alpha particle Radium 223 dichloride in high-risk osteosarcoma: a phase I dose escalation trial

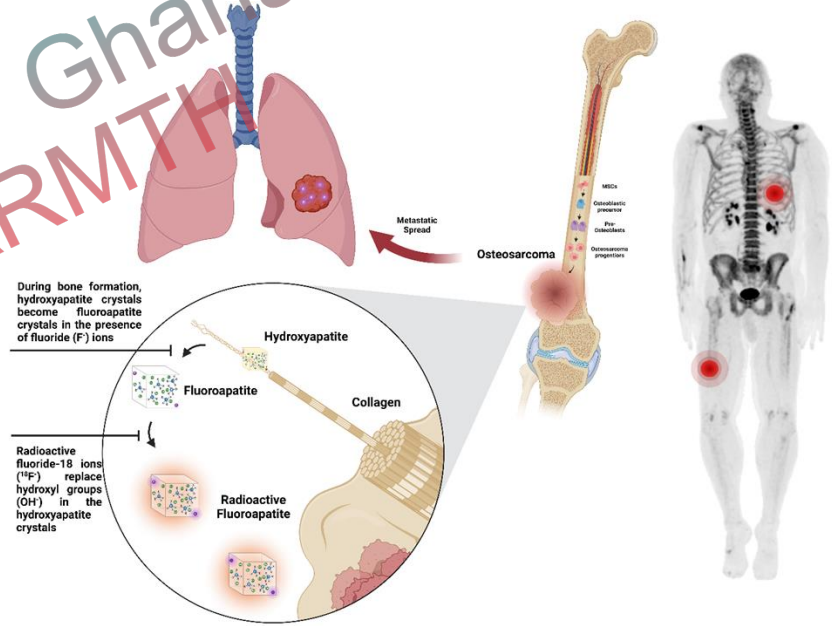
- Among 18 patients enrolled (including 15 males) aged 15-71 years, tumor locations included spine (n=12, 67%), pelvis (n=10, 56%), ribs (n=9, 50%), extremity (n=7, 39%), and skull (n=2, 11%).
- Patients received 1-6 cycles of 223RaCl2; cumulative doses were 6.84-57.81 MBq.
- NaF PET revealed more sites of metastases than did FDG PET. One patient showed a metabolic response on FDG PET and NaF PET. Four patients had mixed responses, and one patient had a response in a brain metastasis. Bronchopulmonary hemorrhage from Grade 3 thrombocytopenia (N=1) was a DLT. The median overall survival time was 25 weeks.

Subbiah, V., et.al. Clin Cancer Res. 2019 Jul 1;25(13):3802-3810.

Alpha particle Radium 223 dichloride in high-risk osteosarcoma: a phase I dose escalation trial

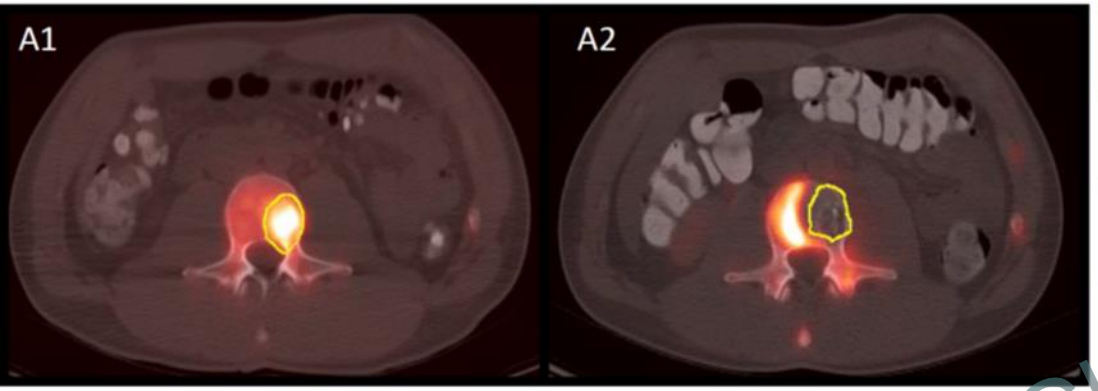
- Dose for 223RaCl2 in osteosarcoma is 100 kBq/kg monthly (twice the dose approved for prostate cancer), with minimal hematologic toxicity, setting the stage for combination therapies.

NAFCIST*



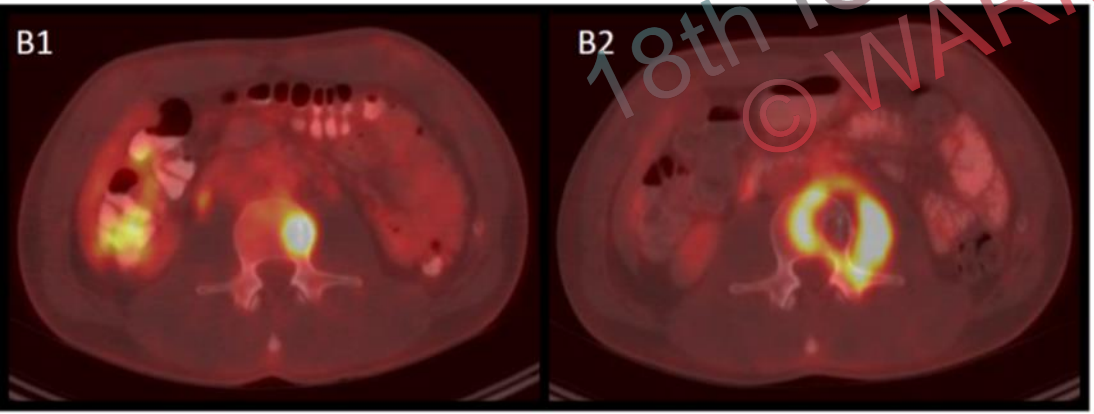
Subbiah, V., et.al. Clin Cancer Res. 2019 Jul 1;25(13):3802-3810.

ESMO in press*



NaF PET-CT best response

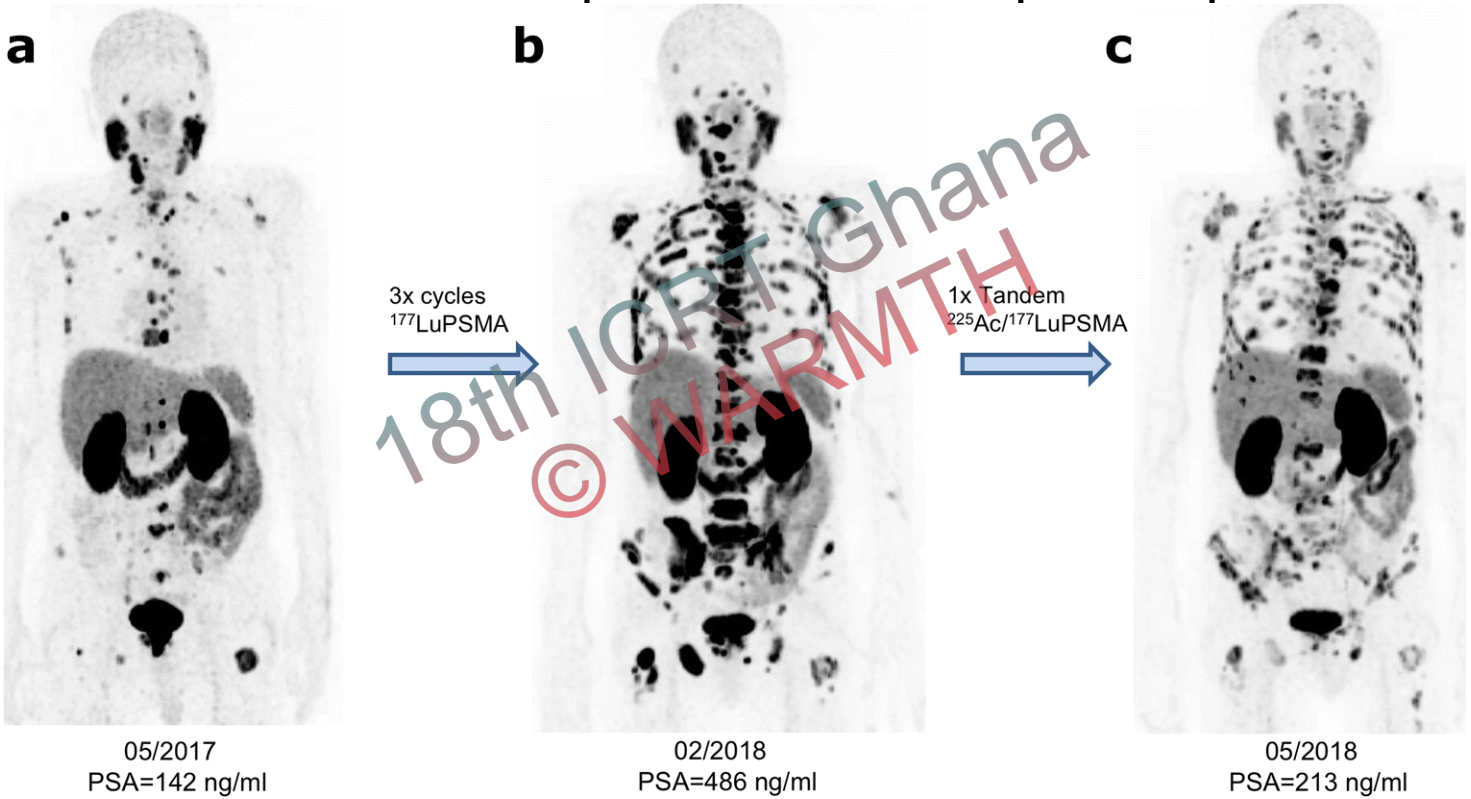
	SUV_{max}	TF_{10}	SUV_{mean}
Baseline	24.05	173.32	12.95
Post-Rx	8.01	17.54	1.46
% △	-66.7%	-89.9%	-88.7%



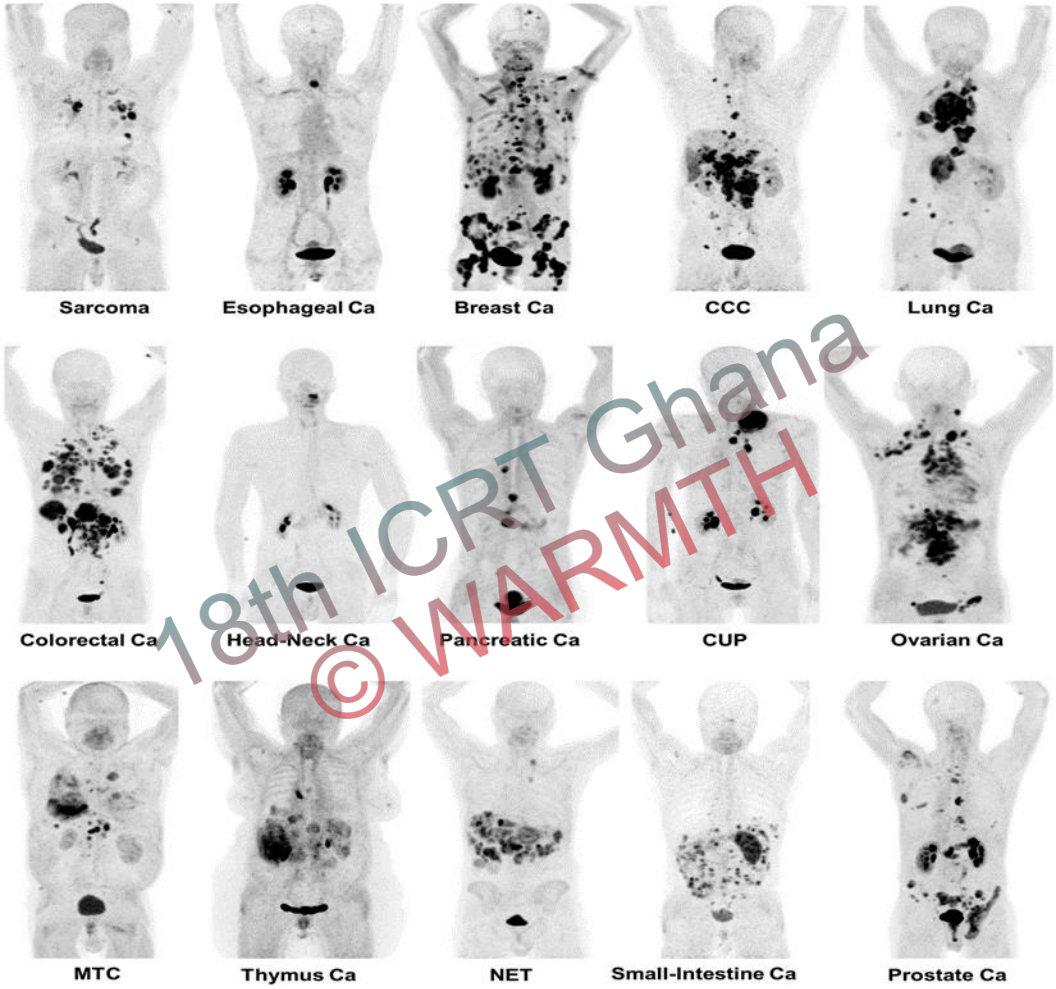
FDG PET-CT best response

	SUV_{max}	TLG
Baseline	12.2	40.8
Post-Rx	2.0	22.1
% △	-83.6%	-45.8%

^{225}Ac-PSMA-617/^{177}Lu-PSMA-617 tandem therapy of metastatic castration-resistant prostate cancer: pilot experience

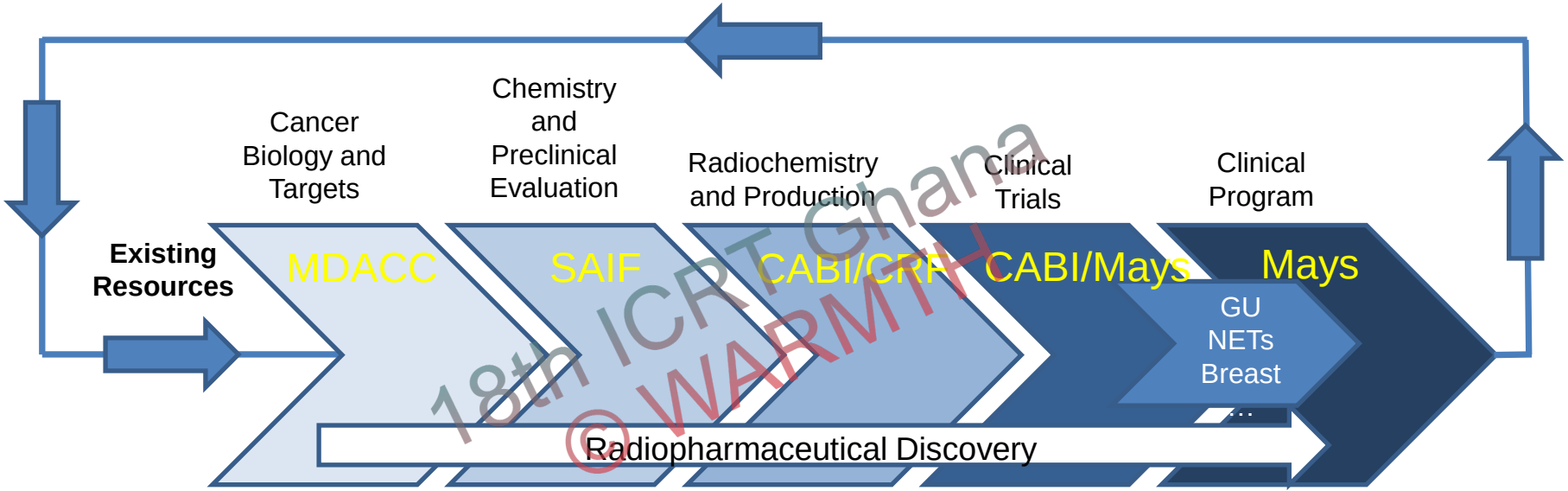


EJNMMI 47, p721–728(2020)

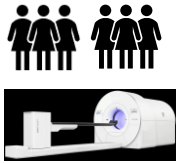


Maximum-intensity projections of 68Ga-FAPI PET/CT in patients reflecting 15 different histologically proven tumor entities (sorted by uptake in descending order). Clemens Kratochwil et al. J Nucl Med 2019;60:801-805

Theranostics Program



Resources Needed



Output Impact

NK/CAR-T cell Rx
Immuno Rx
Radiosensitization

Sequential/combinatorial therapy models.
Microdosimetry modeling

Novel isotope production
High output/efficiency
Target development

First in man imaging
Integrated therapy dosimetry
AI image acquisition analysis

Multidisciplinary Clinical Trials
Early recurrence detection
Intra-therapy response monitoring

Acknowledgements

- Department Nuclear Medicine Faculty and Staff
- Theranostics Program Leads and Members
- Multi-Disciplinary Teams (Thoracic, Endocrine Neoplasia, GU and GI Medical Oncology/Lymphoma).
- Diagnostic Radiology, Imaging Physics, Radiation Oncology
- Cancer Center Support Grant, J E Anderson Endowment

Theranostics Program Development Team

Dr. David Jaffray
Executive Sponsor

Dr. Marshall Hicks
Executive Sponsor

Dr. Homer Macapinlac
Operations Lead

Dr. Charles Manning
Research Lead

Mary Veazie, MBA, CPA
Finance Lead

- Important Contributors

Lee Andrews	Emily Barnhill	Priya Bhosale	Leslie Billings	Kari Brewer Savannah	Kristy Brock	Matthew Campbell
Brian Chapin	Beth Chasen	Paul Corn	Bill Erwin	Anne Fisher	Miriam Flores	Lesley Flynt
Seth Gammon	John Hazle	Tim Heffernan	Donna Hemphill	Jim Incalcaterra	Victoria Johnson	Eric Jonasch
Cheenu Kappadath	Ahmed Kaseb	Eva Kelly	Usman Khaderi	Phillip Koo	Scott Kopetz	Vikas Kundra
Michael Kupferman	Dao Le	Jeffrey Lee	Chun Li	Osama Mawlawi	Richelle Millican	Steven Millward
Elishia Muehe	Jubi Nair	Tinsu Pan	Surendra Prajapati	Gregory Ravizzini	LaChanda Ricks	Jordi Rodon Ahnert
Michelle Ruben	Holly Rumbaugh	Emil Schueler	Nyma Shah	Saima Shaikh	Dan Shoenthal	Janet Sisolak
Jason Stafford	Devaki Surasi	Nancy Swanston	Tim Swenson	Janio Szklaruk	Chad Tang	Sanjit Tewari
Emily Thompson	Wes Vanderhoofven	Aradhana Venkatesan	Stephanie Walters	Richard Wendt	Guofan Xu	Jinzhong Yang
Irene Yu	Amado Zurita-Saavedra					