Future Theranostic Applications: Which diseases hold the greatest promise?

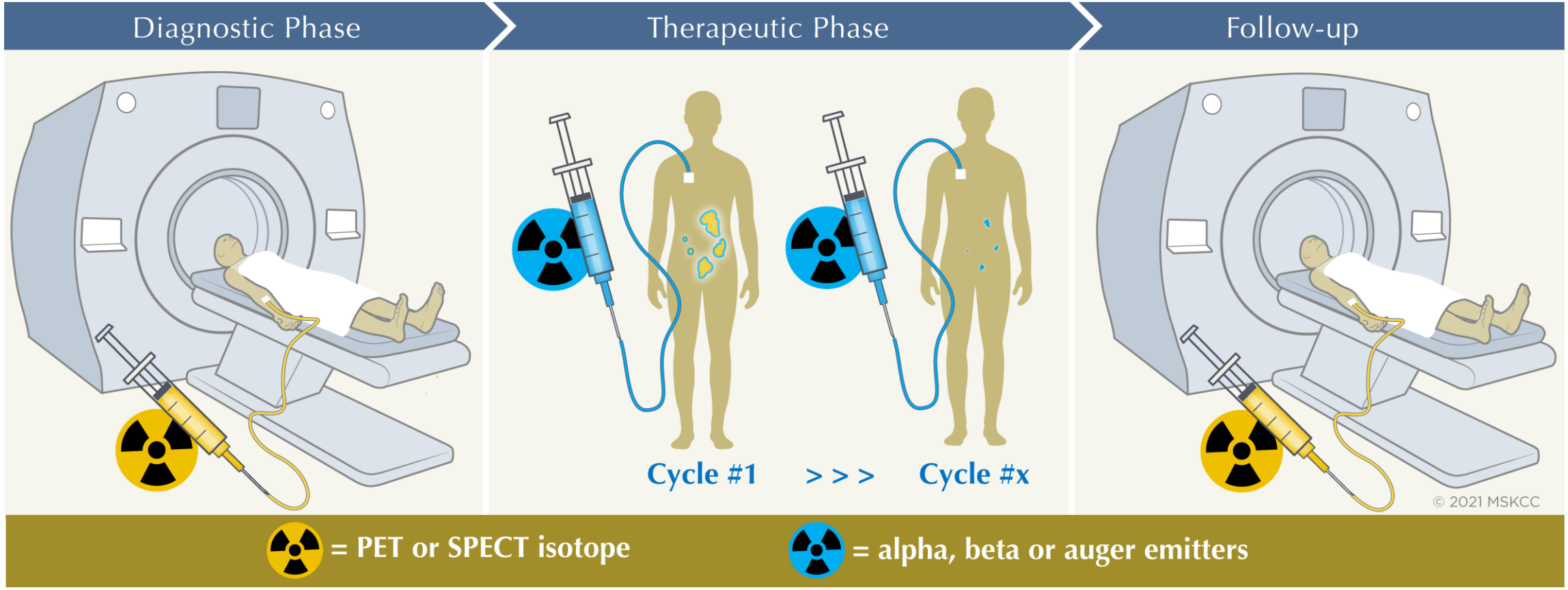
Jason S. Lewis, PhD

Emily Tow Chair in Oncology

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center™

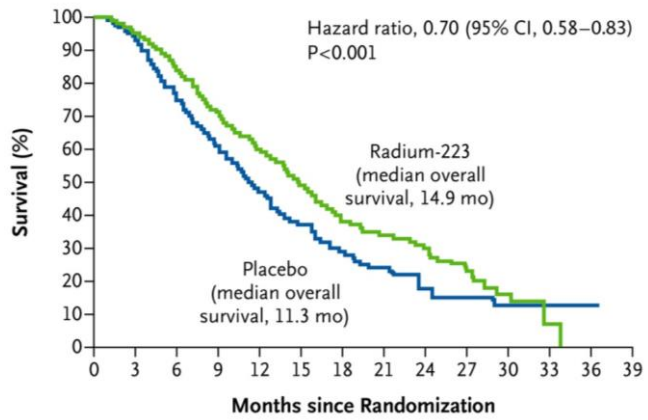
What is a Radiotheranostic?



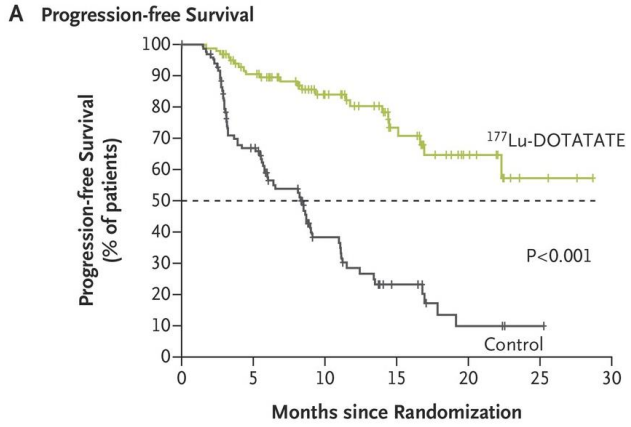
Bodei, Herrmann, Schöder, Scott & Lewis, Nature Reviews Clinical Oncology, 19, 534–550 (2022)

Milestones of Targeted Radiotherapy

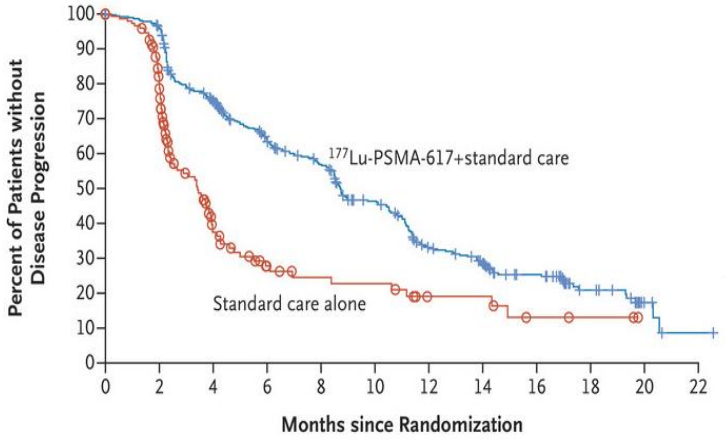
(A) ALSYMPCA



(B) NETTER-1



(C) VISION



2013 — 2017 — 2021

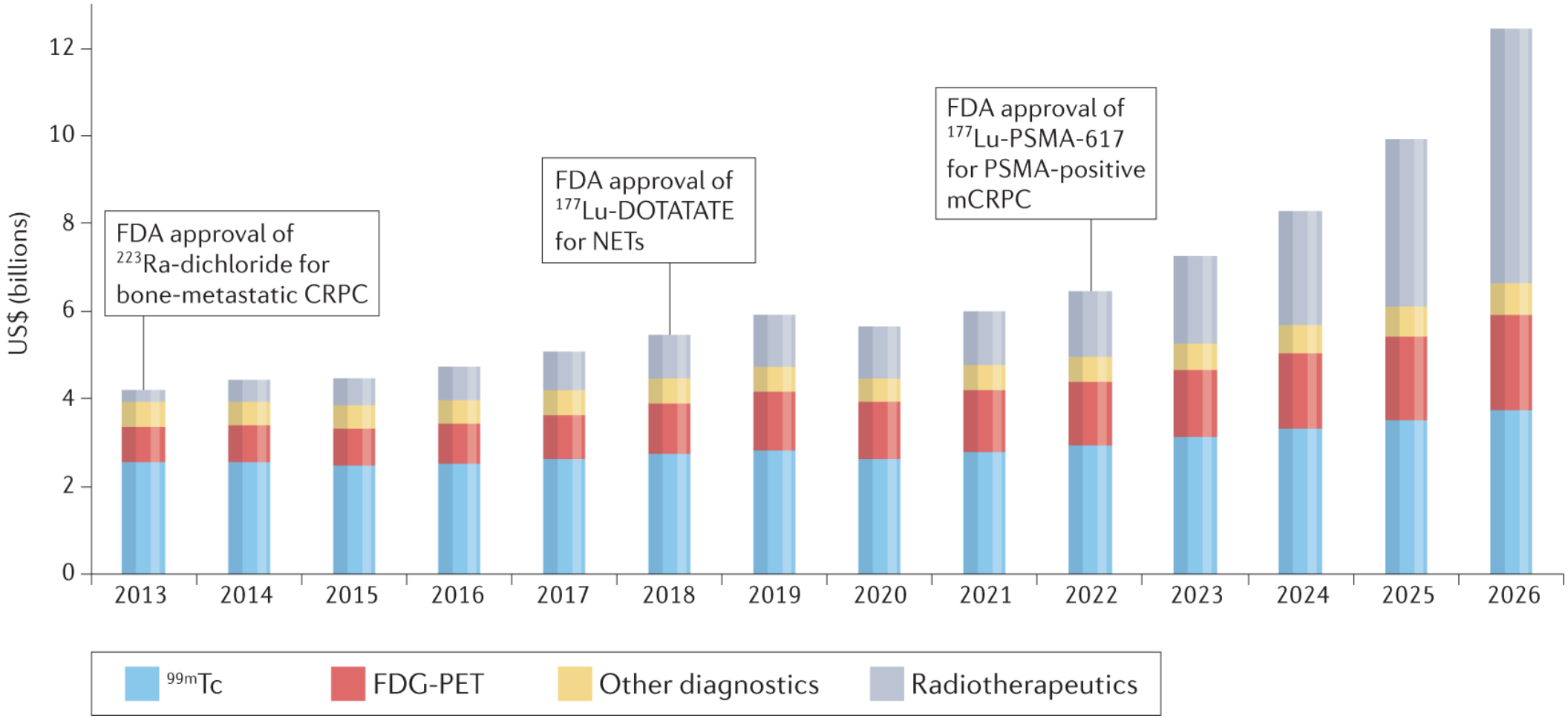
$^{223}RaCl_2$
Parker et al.,
N Engl J Med 2013; 369:213-223

^{177}Lu-DOTATATE
Strosberg et al.,
N Engl J Med 2017; 376:125-135

^{177}Lu-PSMA-617
Sartor et al.,
N Engl J Med 2021; 385:1091-1103

Bodei, Herrmann, Schöder, Scott & Lewis, Nature Reviews Clinical Oncology, 19, 534–550 (2022)

The Predicted Global Nuclear Medicine Market 2013–2026

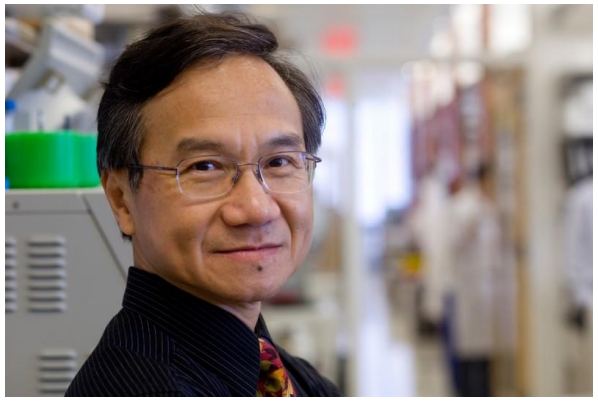


Bodei et al., Nat Rev Clin Oncol, 2022 – Figure 3

MSK Institutional COI: Y-mAbs Therapeutics, Inc.

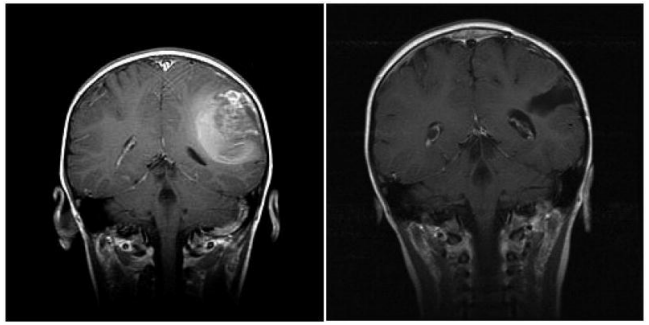
A Curative Approach to Central Nervous System Metastases of Neuroblastoma

K Kramer, BH Kushner, S Modak, N Pandit-Taskar, U Tomlinson, SL Wolden, P Zanzonico, JL Humm, S Haque, MM Souweidane, J Greenfield, EM Basu, SS Roberts, J A Carrasquillo, JS Lewis, SK Lyashchenko, SM Larson, N-KV Cheung

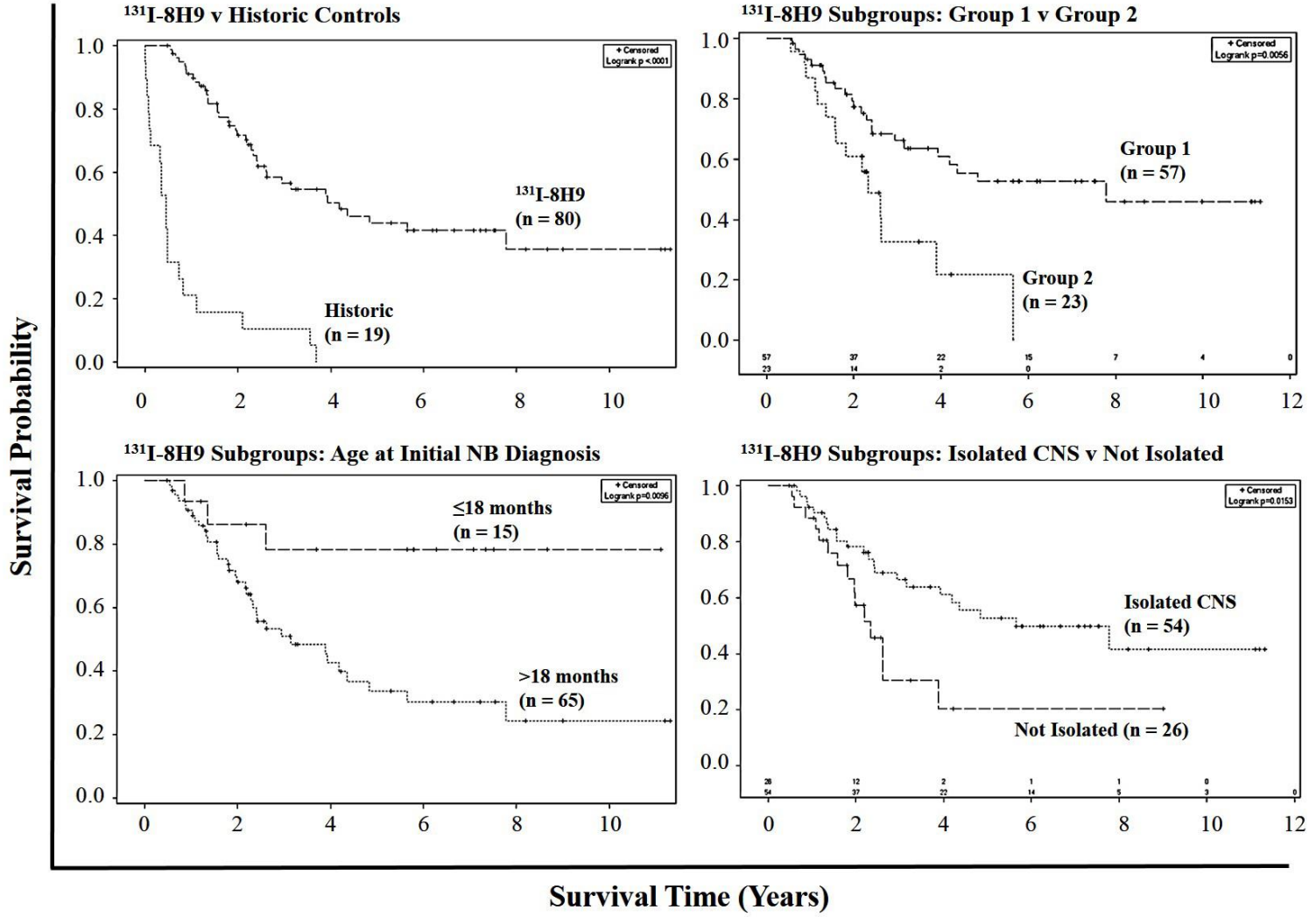


8H9 Monoclonal Antibody (^{131}I-8H9) - results

- 80 patients treated
- 45% alive at 36 months
- 29% alive at >60 months



Kramer, et al. J. Neurooncol. 2010 May

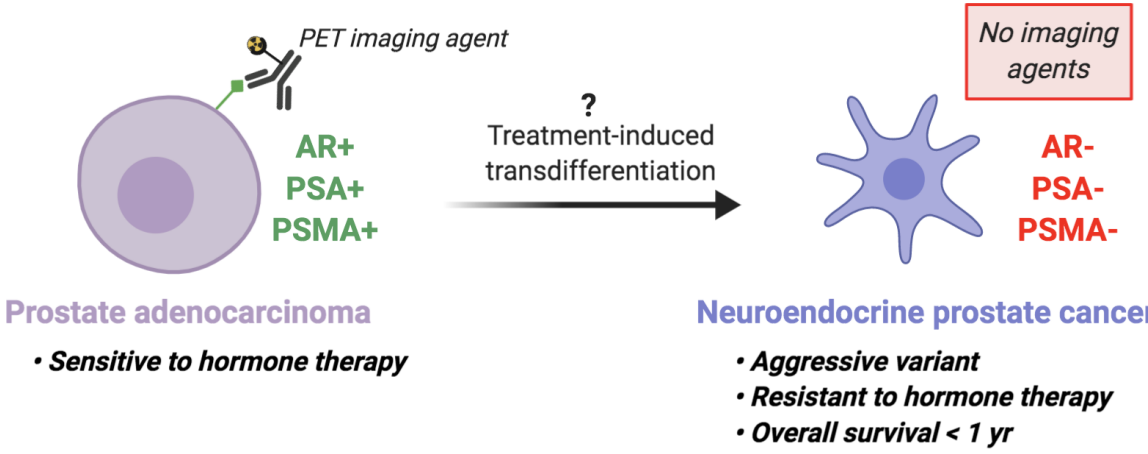


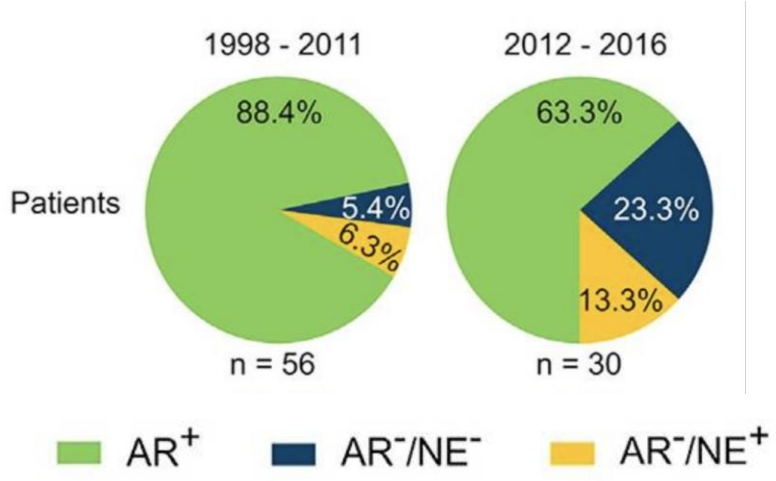
Kramer et al.,

Memorial Sloan Kettering Cancer Center

So what's new?

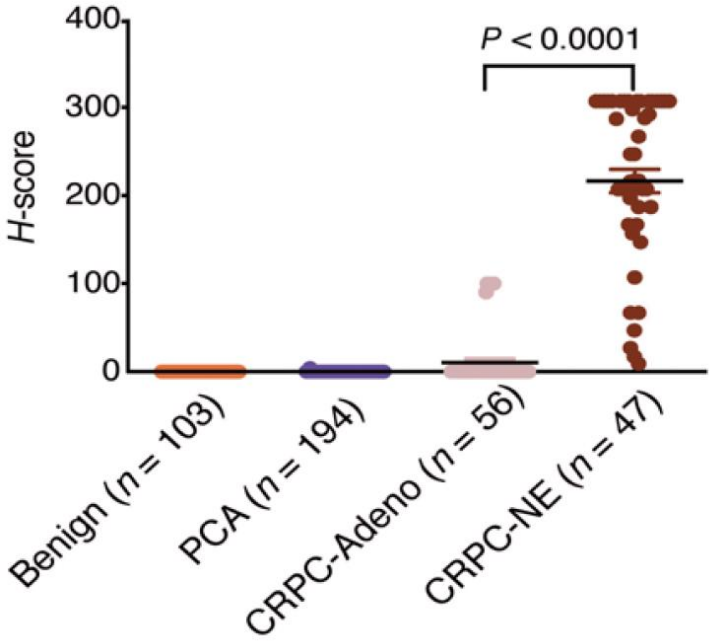
Neuroendocrine Prostate Cancer (NEPC) biologically lethal, biologically diverse and heterogeneous, and pretty much untreatable.





Nelson *et al. Cancer Cell* **2017**

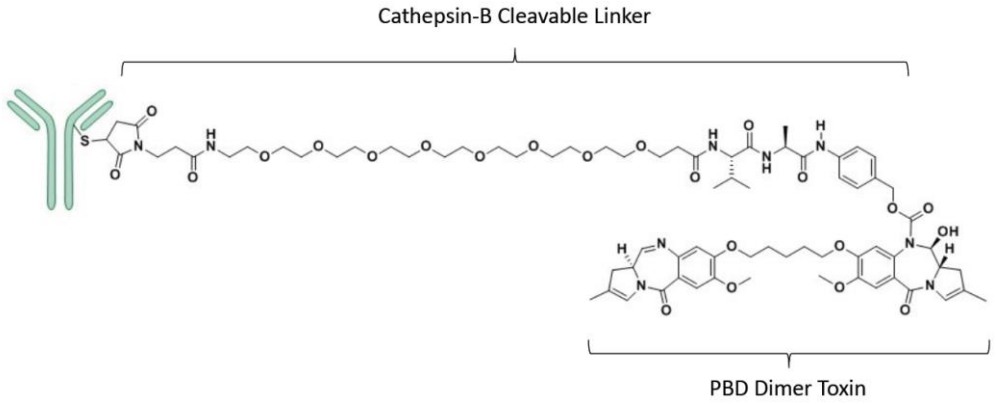
CRPC = Castration resistant prostate cancer

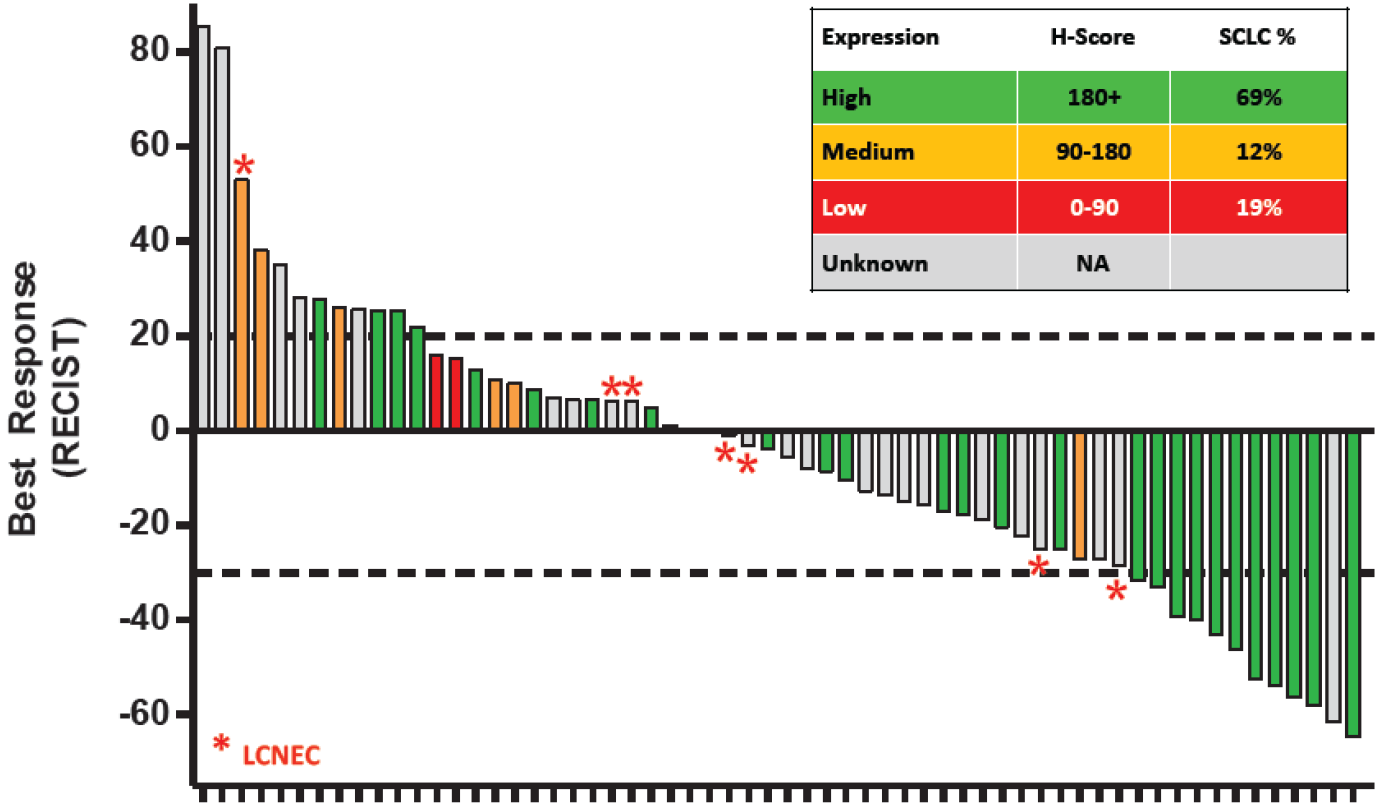


Adeno: detectable by AR tracers
NEPC: Undetectable by AR tracers

Puca *et al. Sci. Transl. Med.* **2019**

Clinical Response Data - Rova-T - targeting DLL3





Expression	H-Score	SCLC %
High	180+	69%
Medium	90-180	12%
Low	0-90	19%
Unknown	NA	

Rudin et al., World Lung 2015

^{89}Zr-SC16 is the first PET scan tracer for detecting and quantifying in vivo tumor DLL3 expression

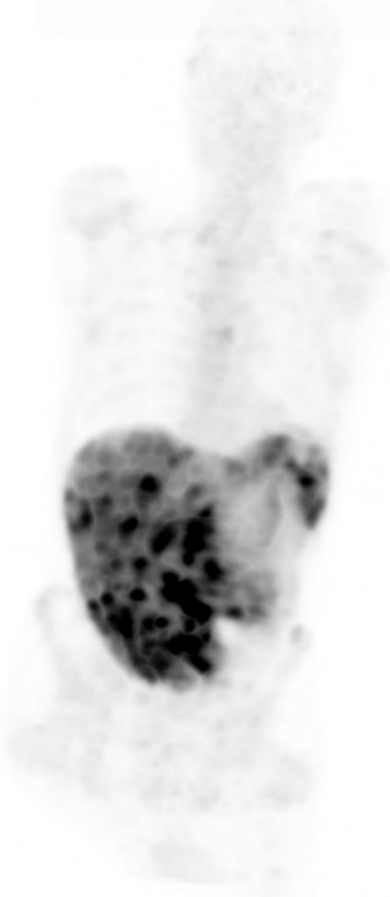
DLL3 PET (3D)

PSMA PET

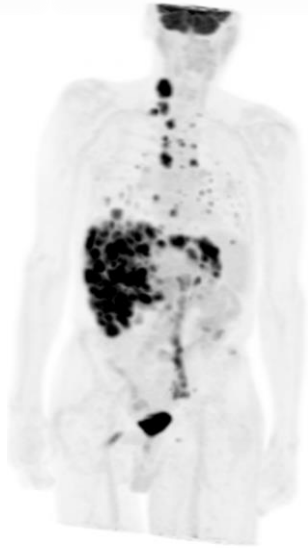
PSMA +ve & DLL3 +ve lesions
PSMA -ve & DLL3 +ve lesions

64-year-old male with prostate adenoCA and biopsy-proven small cell metastasis

DLL3 PET (3D)



FDG PET



63-year-old male with prostate adenoCA and biopsy-proven metastatic high-grade carcinoma with neuroendocrine dedifferentiation metastasis

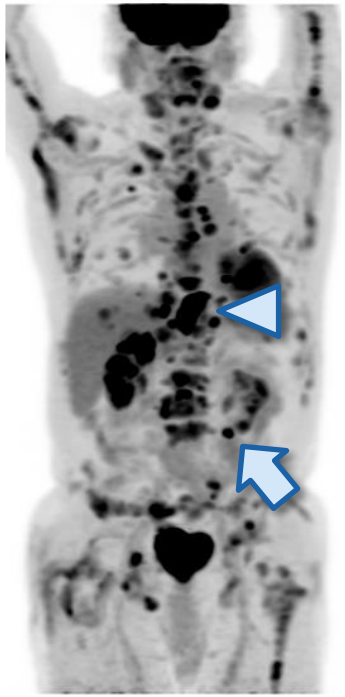
^{89}Zr-SC16 is the first PET scan tracer for detecting and quantifying in vivo tumor DLL3 expression

DLL3 PET (3D)

81-year-old male

- prostate adenoCA
- Biopsy-proven small cell nodal metastasis

Nodal met **Perinephric implant**



FDG PET/CT

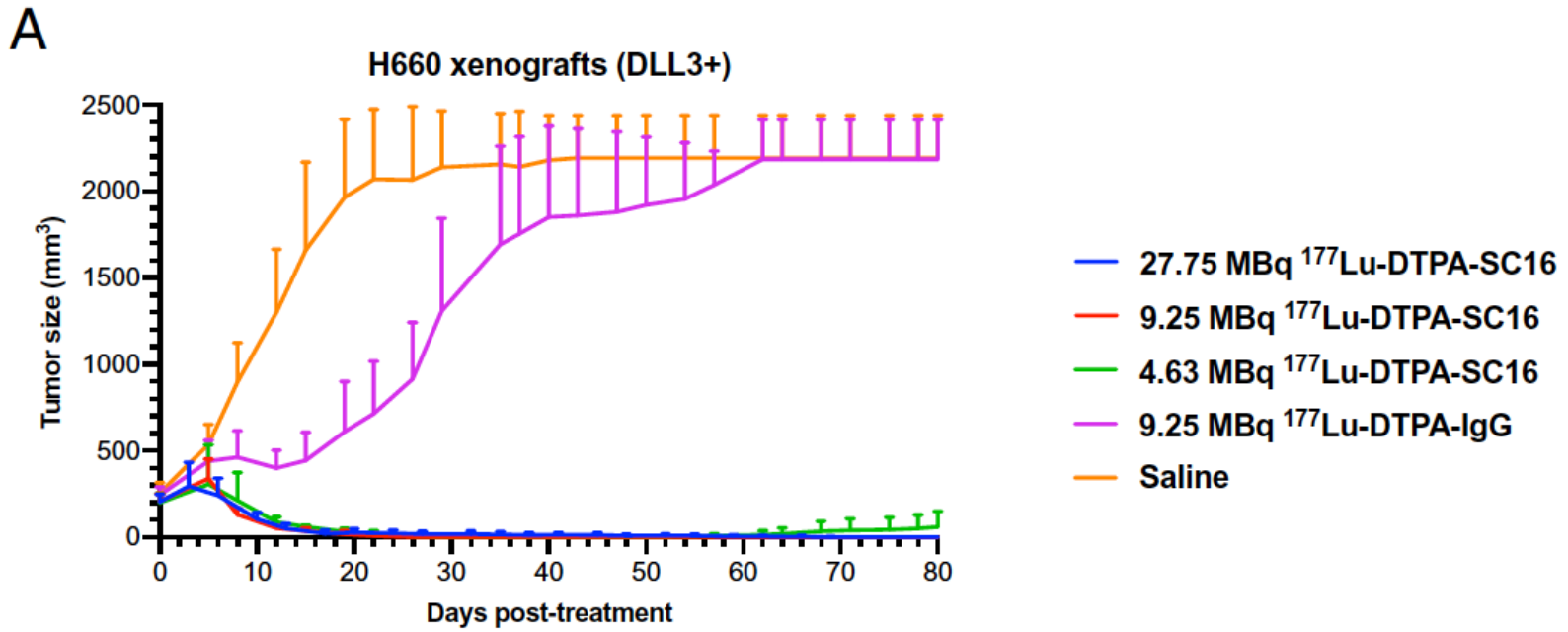
NEPC

Resistant to hormone therapy

Overall survival <1 year

Dunphy et al., data not published

NEPC lesions show *complete* and *durable* tumor regression with ^{177}Lu-SC16



Deep and durable complete pathological responses!

PNAS RESEARCH ARTICLE | APPLIED BIOLOGICAL SCIENCES OPEN ACCESS

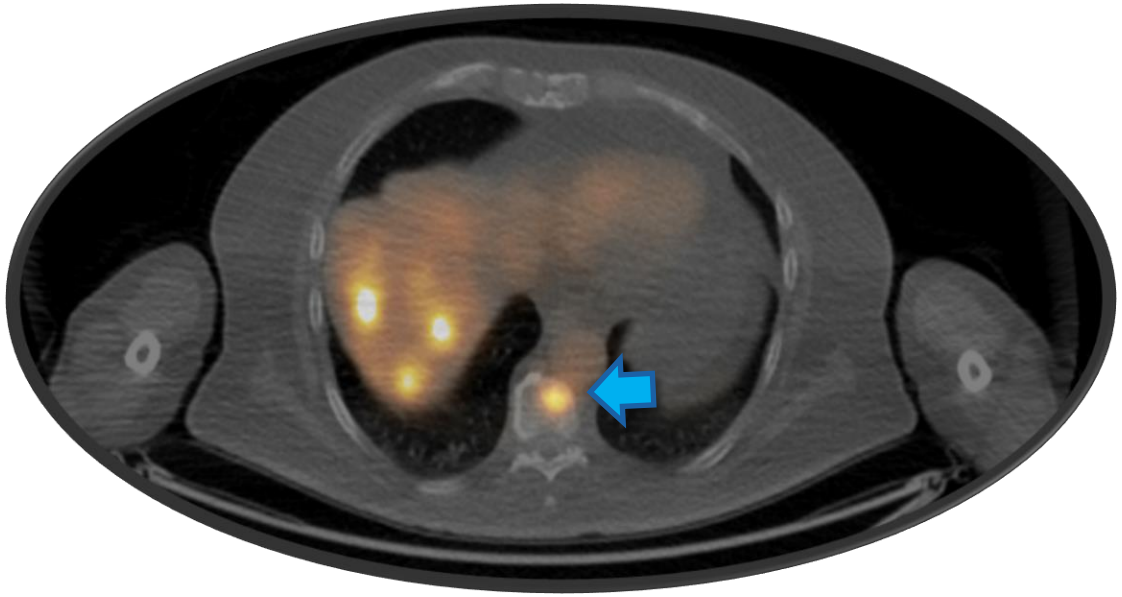
Delta-like ligand 3–targeted radioimmunotherapy for neuroendocrine prostate cancer

Joshua A. Korsen[a,b], Julia A. Gutierrez[a], Kathryn M. Tully[a,b], Lukas M. Carter[a], Zachary V. Samuels[a], Samantha Khitrov[a], John T. Poirier[c], Charles M. Rudin[b,d,e], Yu Chen[d,f], Michael J. Morris[d,g], Lisa Bodei[a], Nagavarakishore Pillarsetty[a,1], and Jason S. Lewis[a,b,e,1]

Edited by Michael Phelps, University of California, School of Medicine, Los Angeles, CA; received March 7, 2022; accepted May 23, 2022

DLL3 expression in SCLC - Zr-89 SC16 PET imaging (19-292 Dunphy, PI; Rudin co-PI)

DLL3 tracer-avid metastases detected in the brain, liver and skeleton. For example, T9 vertebral metastasis (dark blue arrow) with SUV 29.8; and left lobar hepatic metastasis (light blue arrow) with SUV 68.6



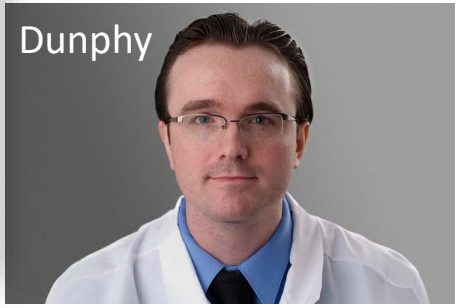
SC16 PET/CT

5dd post tracer-injection

70 yo stage IV SCLC

5 day post tracer-injection

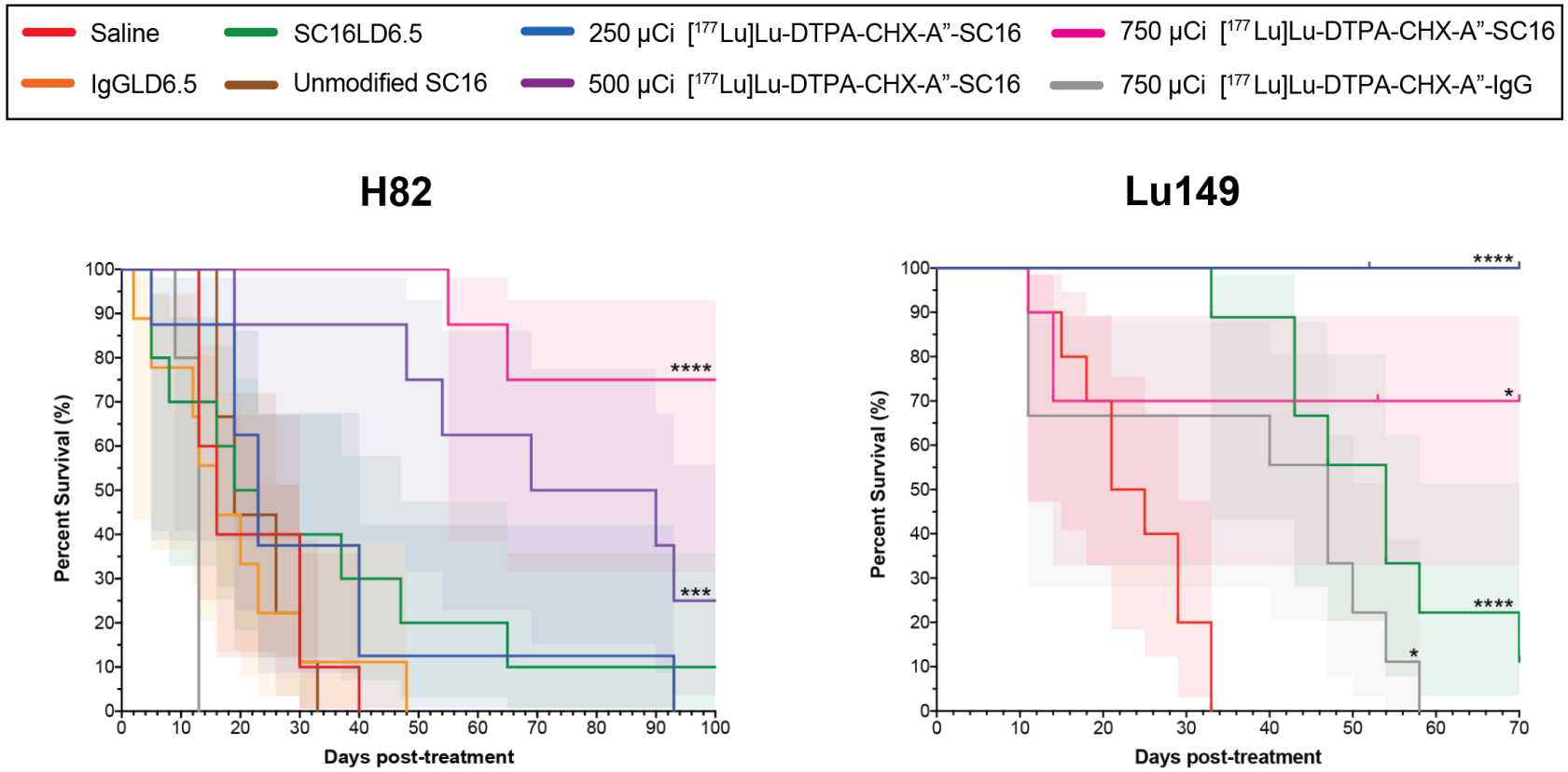
NCT04199741



Dunphy et al., data not published

Radioimmunotherapy targeting DLL3 in SCLC

^{177}Lu-SC16 leads to significantly longer survival in radioresistant (H82) and radiosensitive (Lu149) models



Tully et al., CCR, 28, 1391-1401, 2022

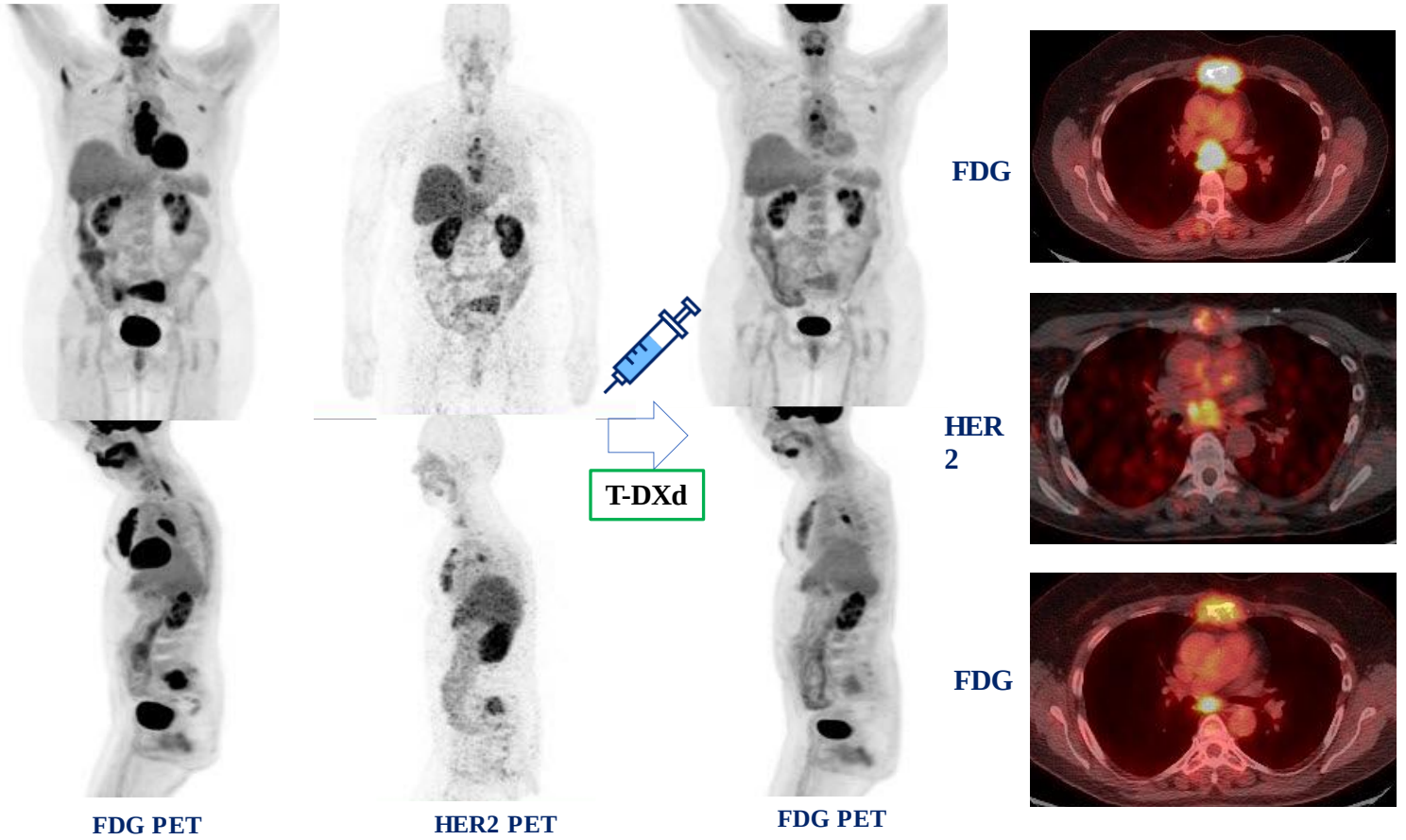
^{89}Zr-pertuzamab for Imaging Her-2 low Cancer

The NEW ENGLAND JOURNAL of MEDICINE

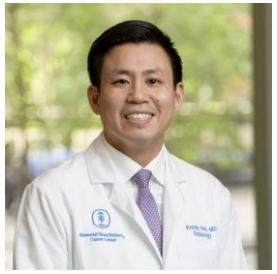
ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

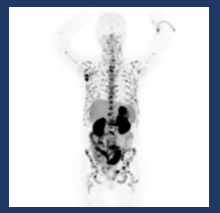


Yeh et al., data not published

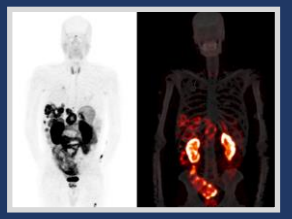


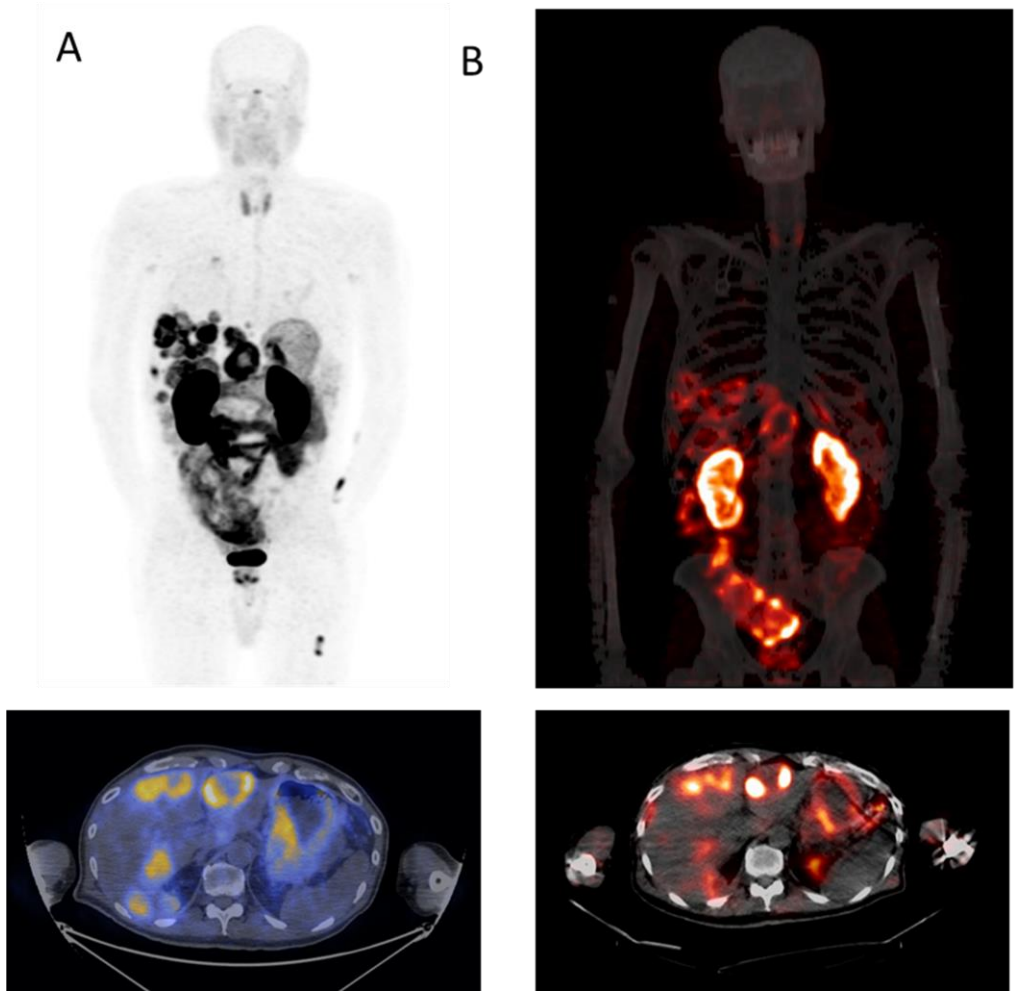
2007

2016



2022





UCDAVIS
UNIVERSITY OF CALIFORNIA

Sutcliffe et al. Henry N. Wagner, Jr., Image of the Year 2023

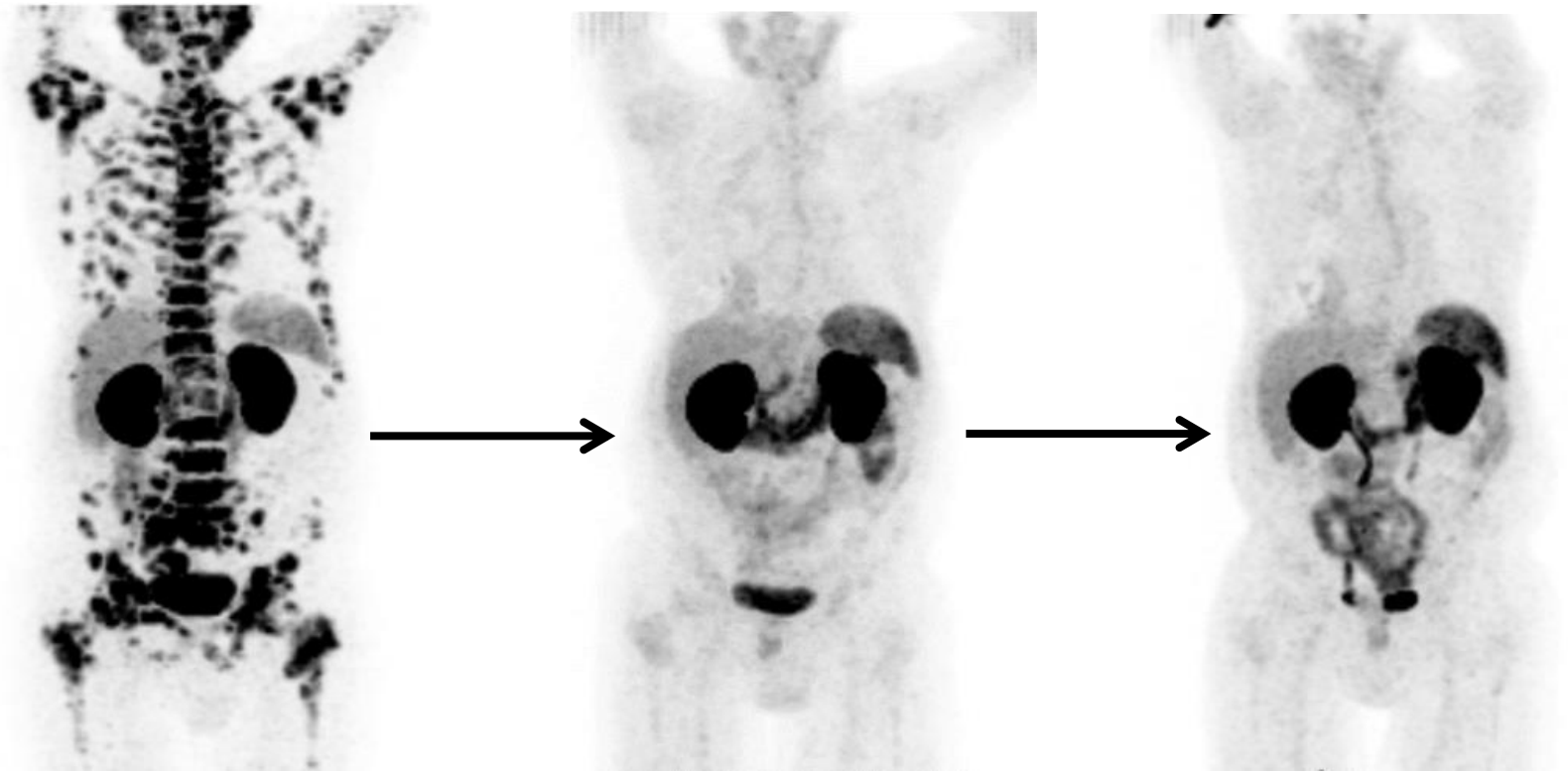
LUSTGARTEN FOUNDATION
PANCREATIC CANCER COLLECTIVE
STAND UP TO CANCER

Why Alpha Radiopharmaceuticals?

- Alpha radiation is ~100 times more potent than other forms of radiation, therefore able to overcome some common tumor resistance.
- With alpha emitters, the highly effective energy deposition can kill individual targeted tumor cells (including micrometastases) by causing direct DNA double strand breaks, irrespective of the cell mitotic status or oxidative state, or ROS.
- Alpha radiation energy is deposited over approximately one to three cell diameters (the healthy surrounding tissues are therefore largely spared from damage). This is particularly important in pediatric and heavily pre-treated adult patients.

PSMA-directed Alpha Therapy – induces complete remissions *after all prior therapies* have been used

^{225}Ac-PSMA



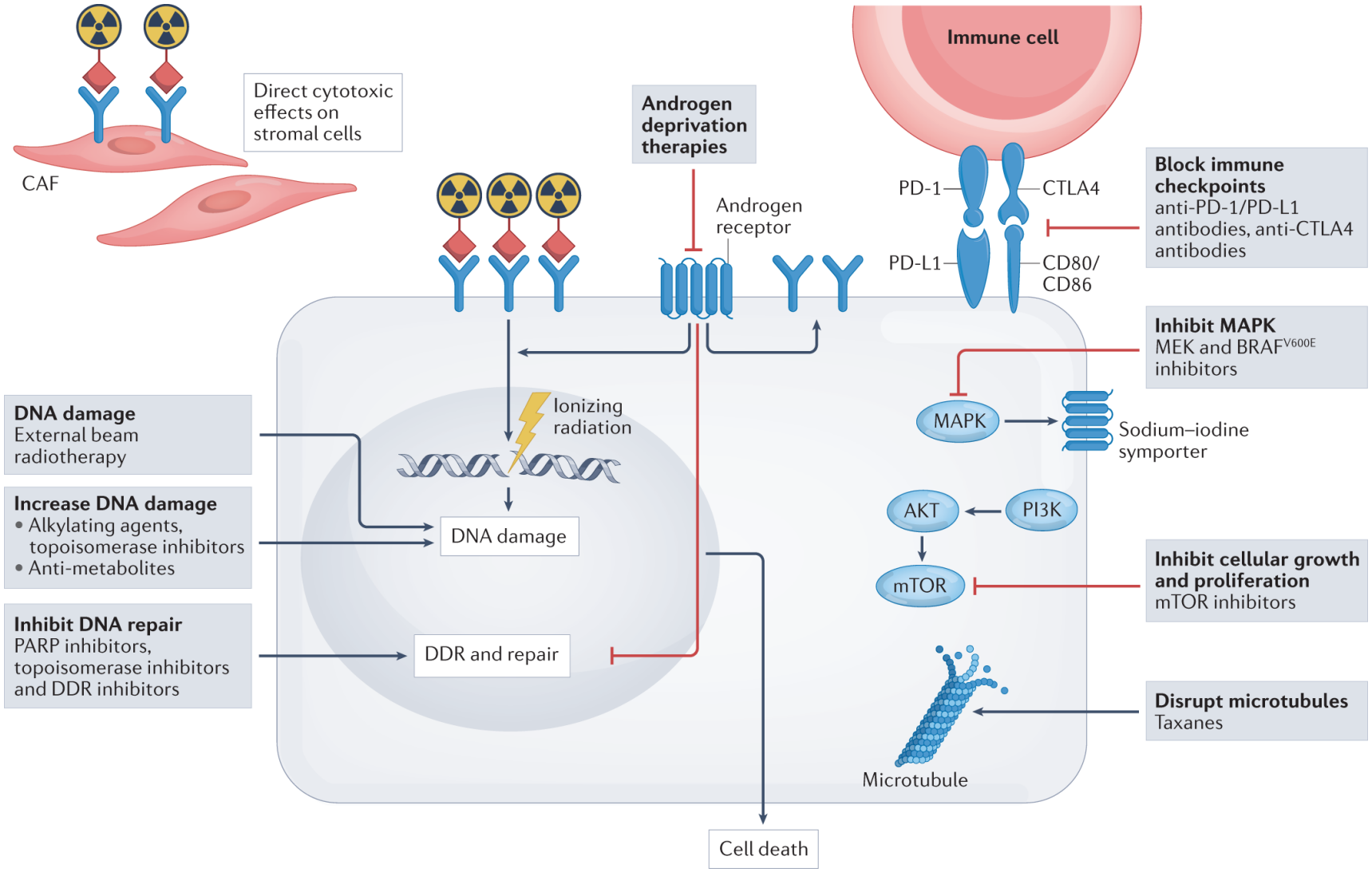
PSA = 2923 ng/ml

PSA = 0.26 ng/ml

PSA < 0.1 ng/ml

Zechmann CM, et al. Eur J Nucl Med Mol Imaging. 2014

Therapeutic Approaches Involving Radiotheranostics



Bodei et al., Nat Rev Clin Oncol, 2022 – Figure 4

Conclusions and Thoughts

- Theranostics may have application in numerous indications
- Need to develop applications in combination with other treatment modalities
- The growth and expansion in the field is unprecedented – but there are significant challenges in the future e.g., workforce shortages and lack of redundancy in supply chain

Thank You!