NCI Workshop on Systemic Radiopharmaceutical Therapy April 19,20, 2018

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Rosen Chair and Lab Head

Memorials Slona Kettering Cancer Center and Sloan Kettering Institutee

High Dose I-131 Therapy of Thyroid Cancer at MSKCC

1. Ablation post-thyroid cancer removal
2. Treatment of Metastatic Disease

Radioactive Iodine-131

- Effective Therapy in Well differentiated Thyroid Cancer
- Ablation post-surgery
- Treatment of Metastatic Disease
- Prognosis of Non-Iodine Avid Disease is Poor

^{131}I Therapy and RAI Resistance (RAIR) in Well differentiated Thyroid Ca

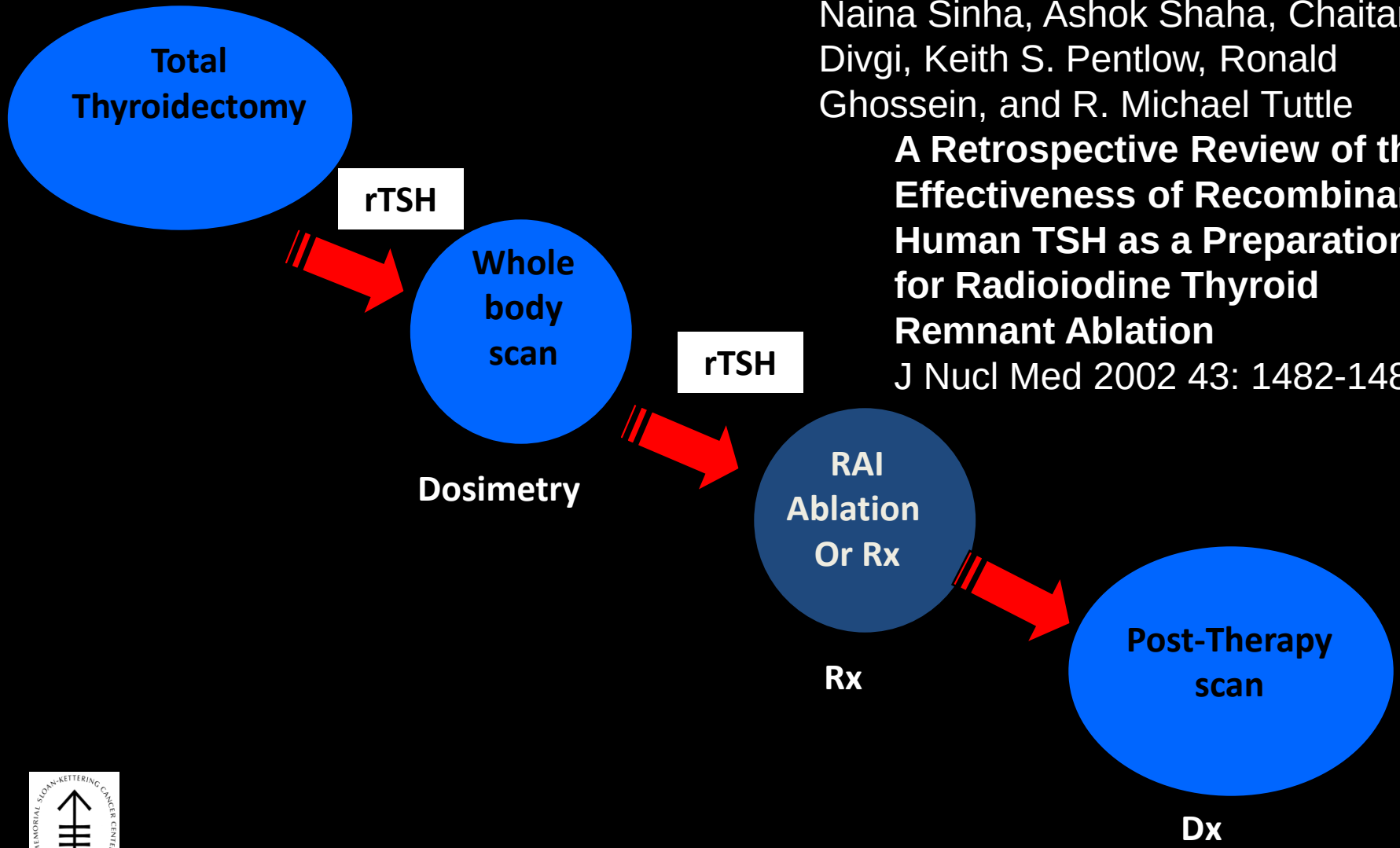
- Dosimetry: strongly recommended for tumor and normal organs
- Key Role for Theranostic Pair: ^{124}I/^{131}I
- Re-differentiation with TKI inhibitors
- Dosimetry and Precision Medicine: Role for Directed Biopsy

MSKCC Practice Guidelines

Richard J. Robbins, Steven M. Larson, Naina Sinha, Ashok Shaha, Chaitanya Divgi, Keith S. Pentlow, Ronald Ghossein, and R. Michael Tuttle

A Retrospective Review of the Effectiveness of Recombinant Human TSH as a Preparation for Radioiodine Thyroid Remnant Ablation

J Nucl Med 2002 43: 1482-1488



Molecular Imaging for the study of Radioiodine Resistance (RAIR) in Thyroid Cancer

Iodne-124 (^{124}I)

2-flouro-2-(D-deoxy-glucose) (FDG)

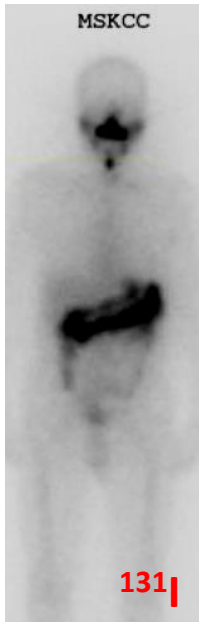


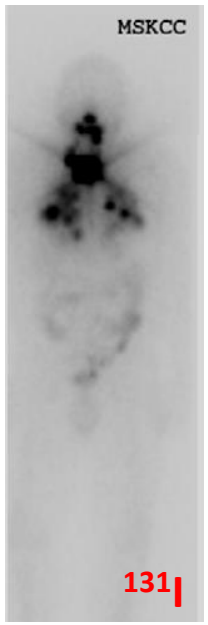
The Clinical Problem: RAI-Refractory Thyroid Cancer

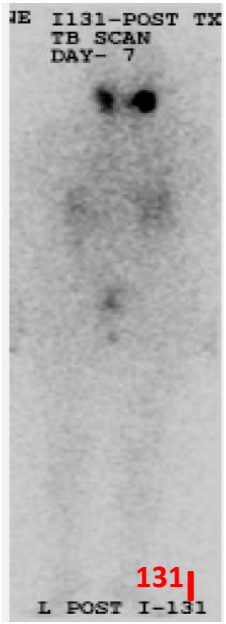
- Distant metastases are the most frequent cause of death for patients with differentiated thyroid cancer[1]
- Decreased RAI incorporation into metastatic sites is associated with higher mortality[2]
- New therapies for RAI-refractory thyroid cancer are desperately needed

Clinical States of Thyroid Cancer: Radioiodine (RAI)

PRIMARY TUMOR	RECURRENT/METASTATIC DISEASE	
	RAI-AVID (RAIA)	**RAI-REFRACTORY (RAIR)**
Thyroidectomy Adjuvant RAI (^{131}I) TSH suppression	RAI Surgery EBRT TSH suppression	Chemotherapy Surgery EBRT TSH suppression







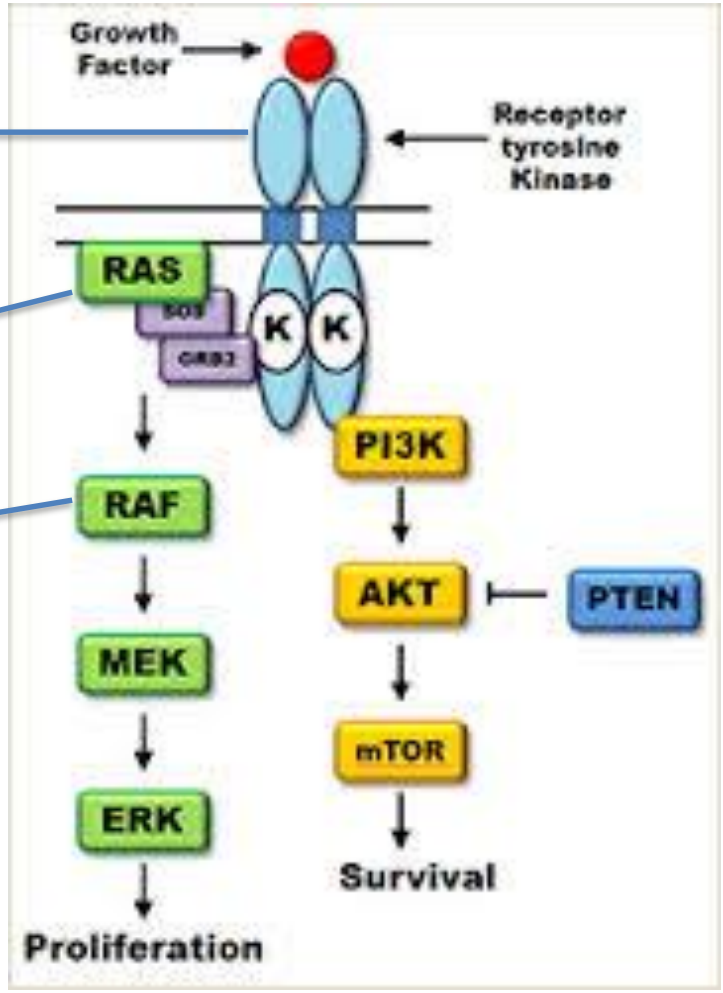
RAIA  RAIR

MAP Kinase Signaling and PapillaryThyroid Cancer (PTC)

RET/PTC in 3/20 patients (15%)

NRAS Q61R and *Q61K* *25% (5/20) patients*

BRAF V600E
45%(9/20) patients



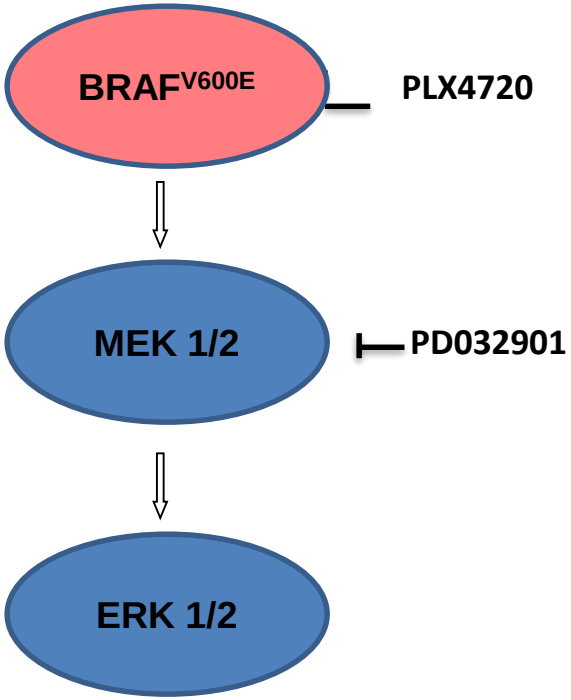
Driver oncogenes are known for ~95% of PTC tumors, and ~75% involve MAPK pathway

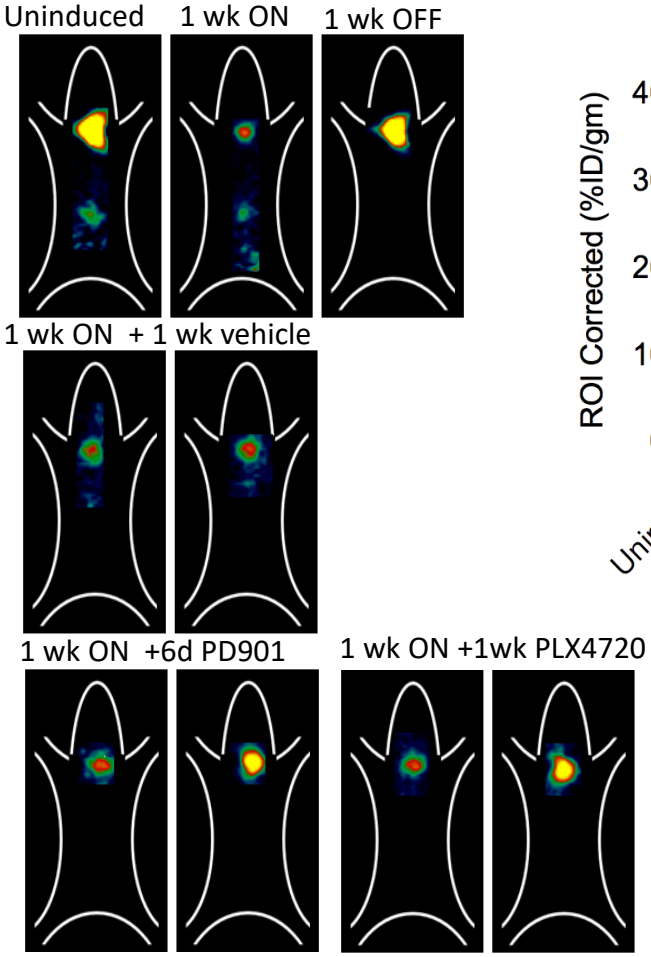
Integrated Genomic Characterization of Papillary Thyroid Carcinoma

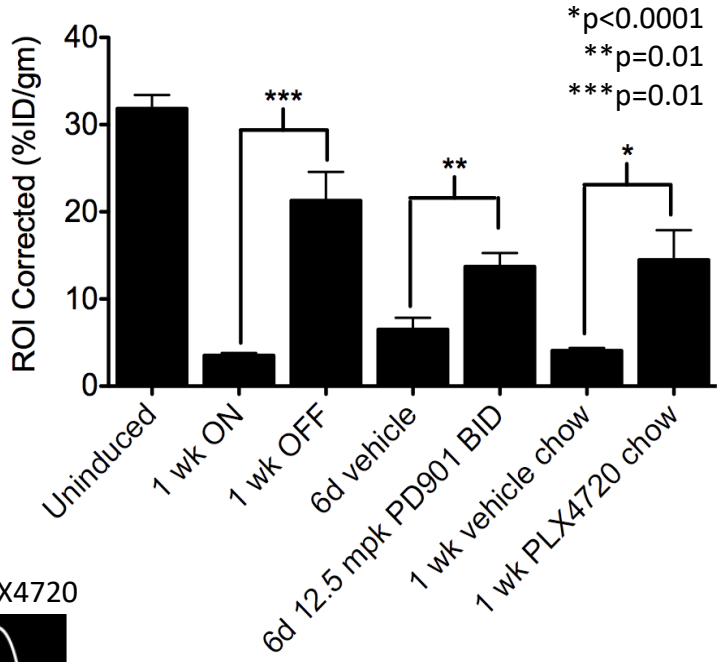
The Cancer Genome Atlas Research Network[1]

Cell 159:676-690, 2014

Pharmacologic inhibition of DOX inducible oncogenic BRAF signaling increases RAI incorporation in mice with thyroid-specific inducible expression of *BRAF^{V600E}* .







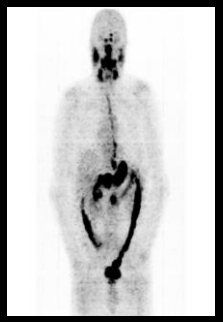
Chakravarty D et al. J Clin Invest 2011

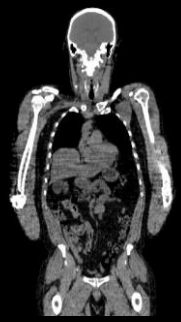
Primary Objective

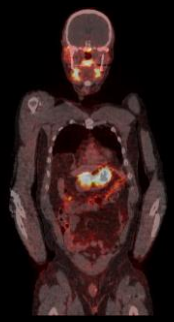
To determine whether RAI incorporation increases in RAI-refractory thyroid cancer metastases after 4 weeks of treatment with a MAPK pathway inhibitor.

Selumetinib (AZD6244 Hyd-Sulfate, ARRY-142886)
Highly selective, allosteric inhibitor of MEK 1/2
Inhibits MEK1 *in vitro* with an IC_{50} of 14.1 +/- 0.79 nM[1]

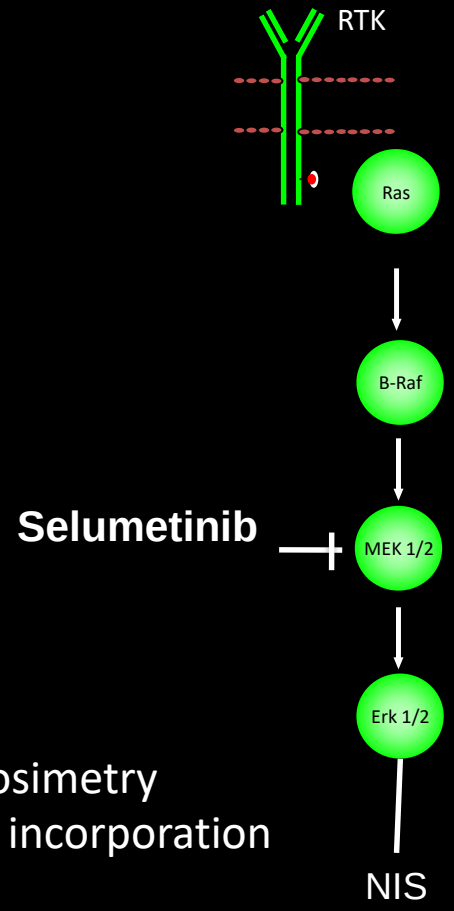
^{124}I –Positron Emission Tomography (PET)/CT


PET images


CT images


Fused images

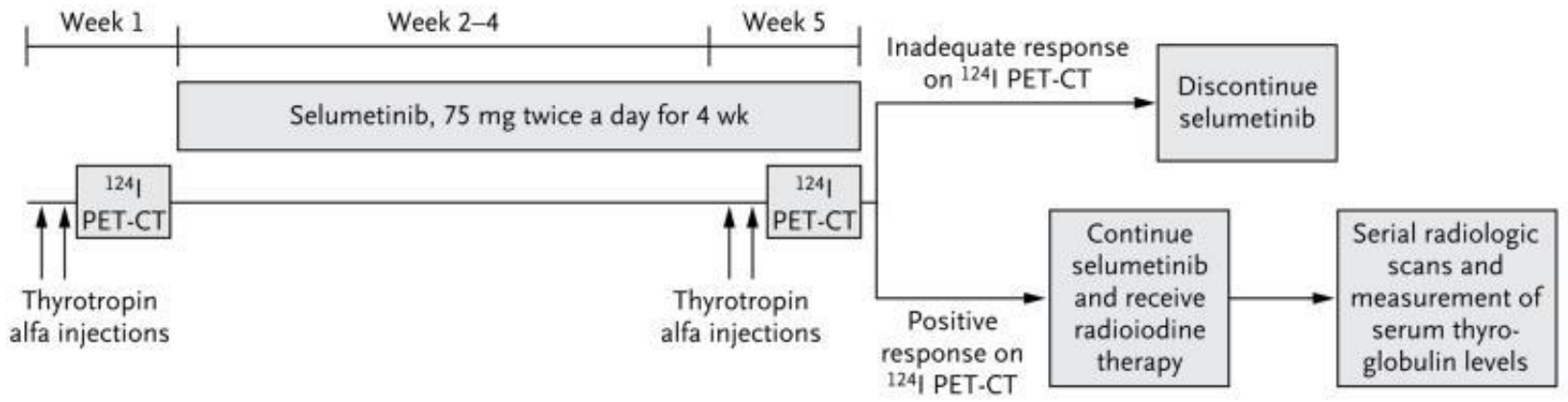
Advantages of ^{124}I –PET
Quantitative, allows lesional dosimetry
Structural correlates for iodine incorporation



Restoring Radiodine Uptake in Thyroid Cancer

Ho et al: N Engl J Med. 2013 Feb 14; 368(7): 623–632.

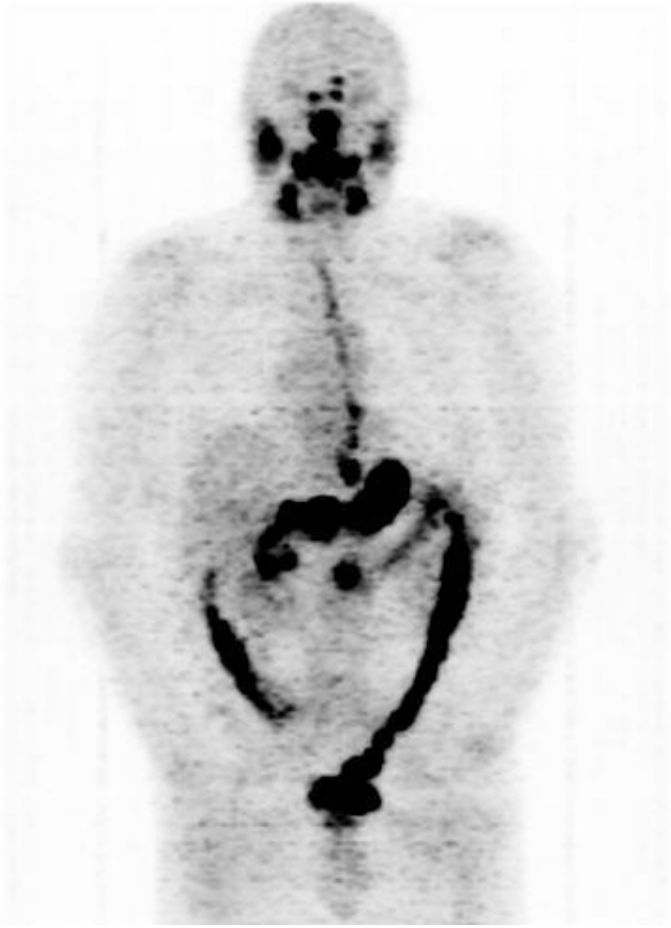
A



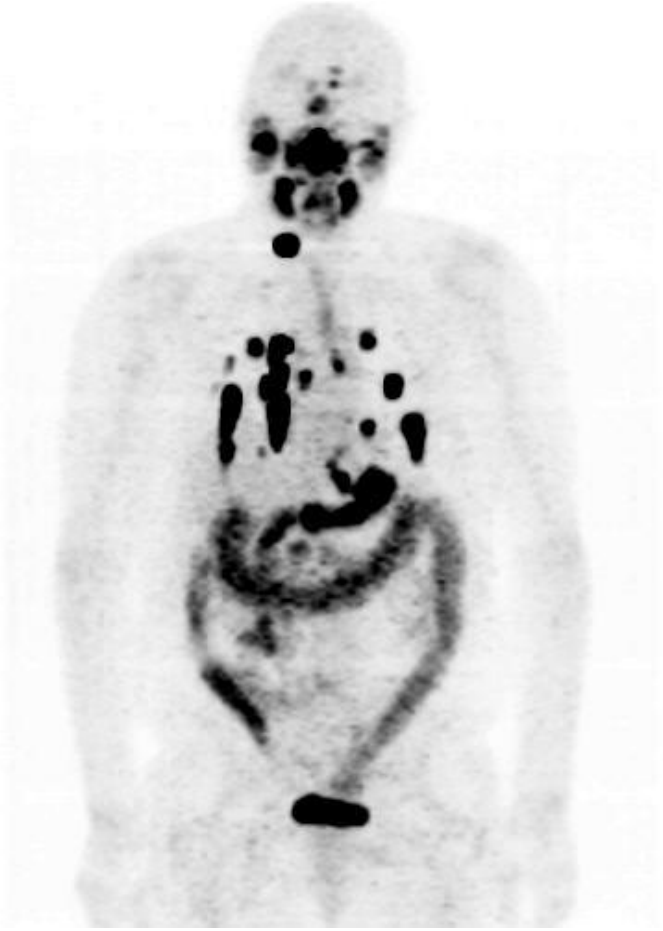
B

Tumor Genotype	Patients with Increased Iodine Uptake in a Lesion after Selumetinib	Patients Who Received Radioiodine
	no./total no. of patients	
BRAF	4/9	1/9
NRAS	5/5	5/5
RET/PTC	2/3	1/3
Wild-type	1/3	1/3
Total	12/20	8/20

^{124}I PET: Selumetinib induces iodine incorporation in a BRAF MUT patient



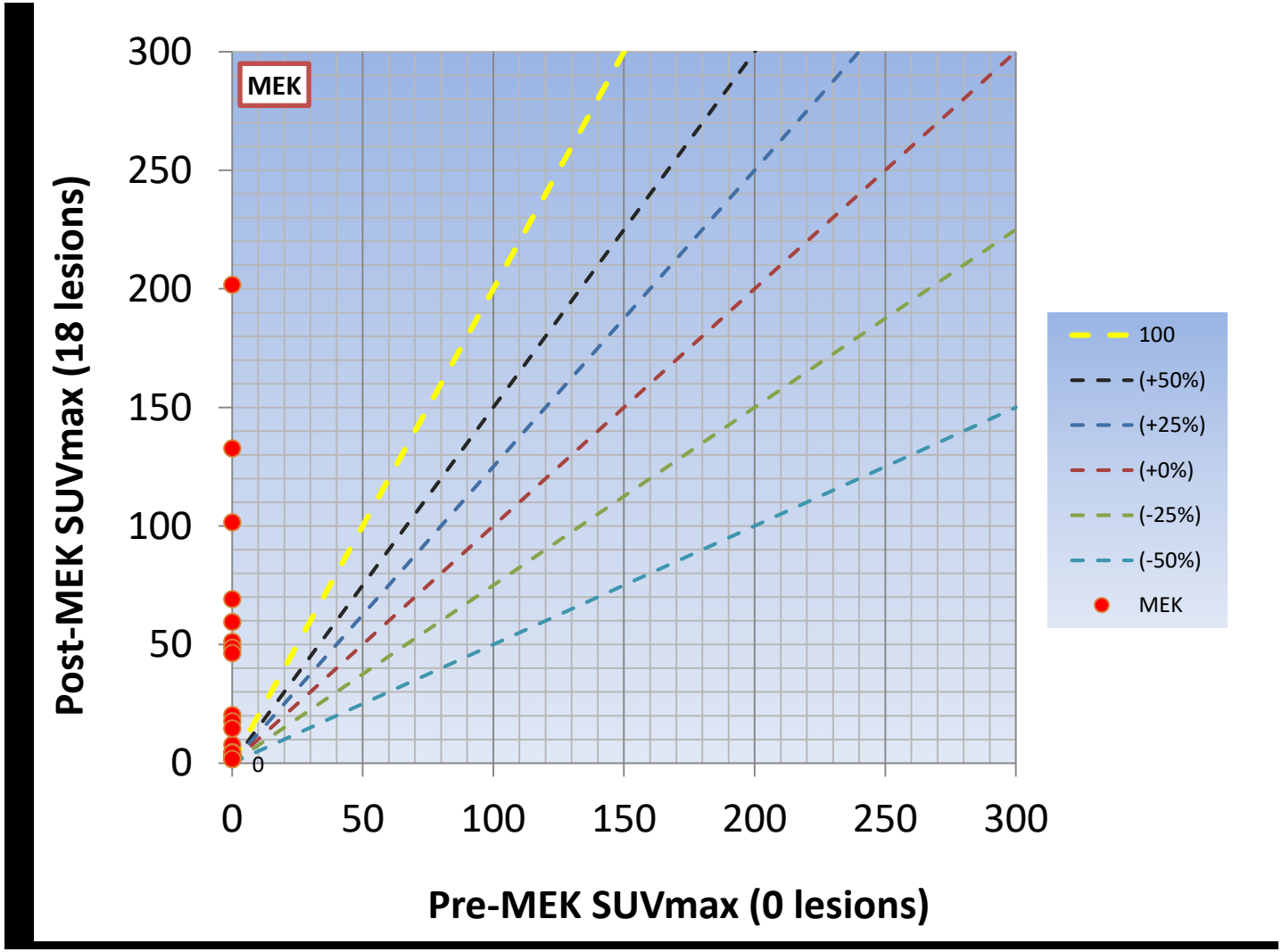
Baseline



Post-Selumetinib

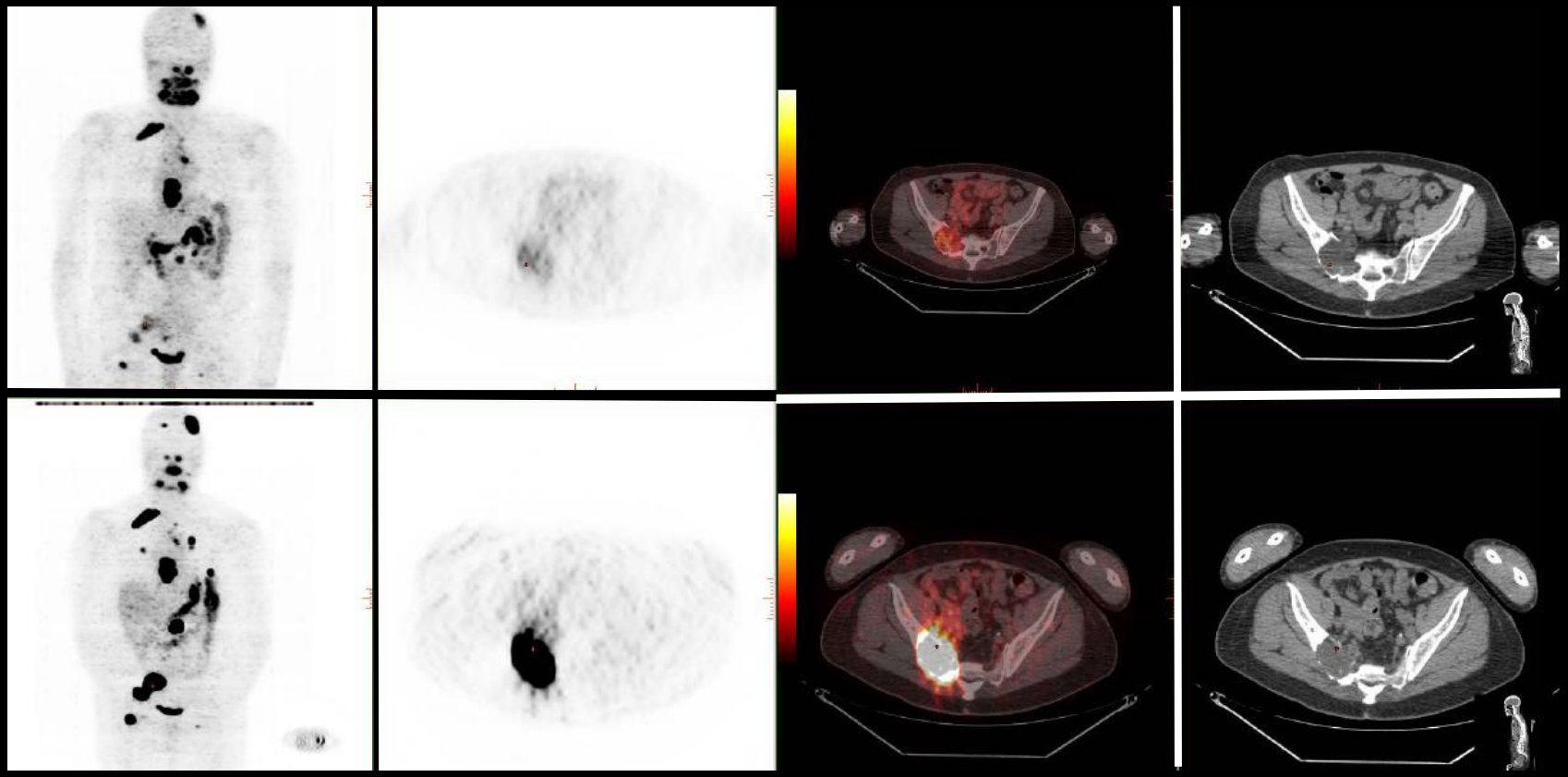
Ravinder Grewal

^{124}I PET Lesional Analysis: Selumetinib induces iodine incorporation in nearly all metastases



Desiree D'Andreis and Ravinder Grewal

^{124}I PET: Selumetinib increases iodine incorporation in bone metastases



Ravinder Grewal and Elmer Santos

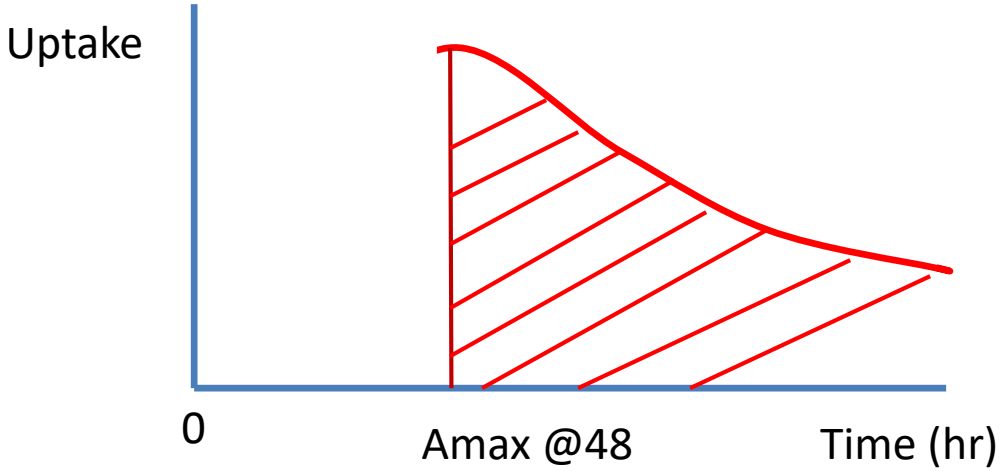
^{124}I for lesion specific dosimetry in thyroid cancer

*Selecting for >2000 cGy lesion dose improved response rate for ^{131}I Rx

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

Simplified dose model

The simplified model relies on the PET information from a single 48hr PET scan.

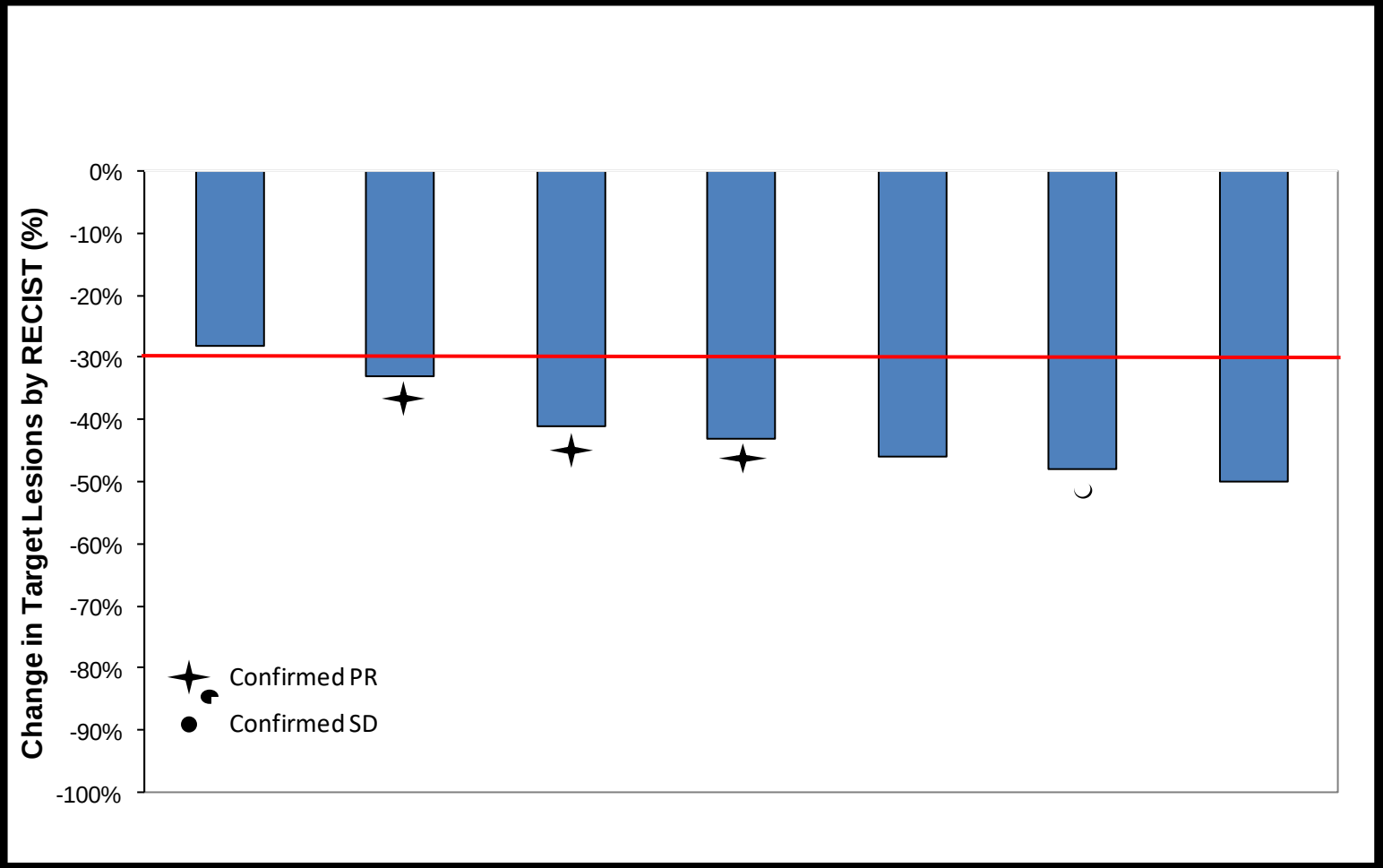


$$\text{Dose (cGy)} = \int \frac{A_{max}}{m} \exp^{-\frac{(0.693 * t)}{\tau_e}} . \Delta\phi$$

where τ_e = 48hr which is an average effective half-life in each lesion and $\Delta\phi$ = 0.405 g.cGy/ µCi.hr which is the equilibrium dose constant.

In can be shown that SUV > 20 would get > 2000 cGy, per lesion for an administered dose of 250 mCi, the usual maximum outpatient treatment dose

RECIST Response For Patients Treated with RAI

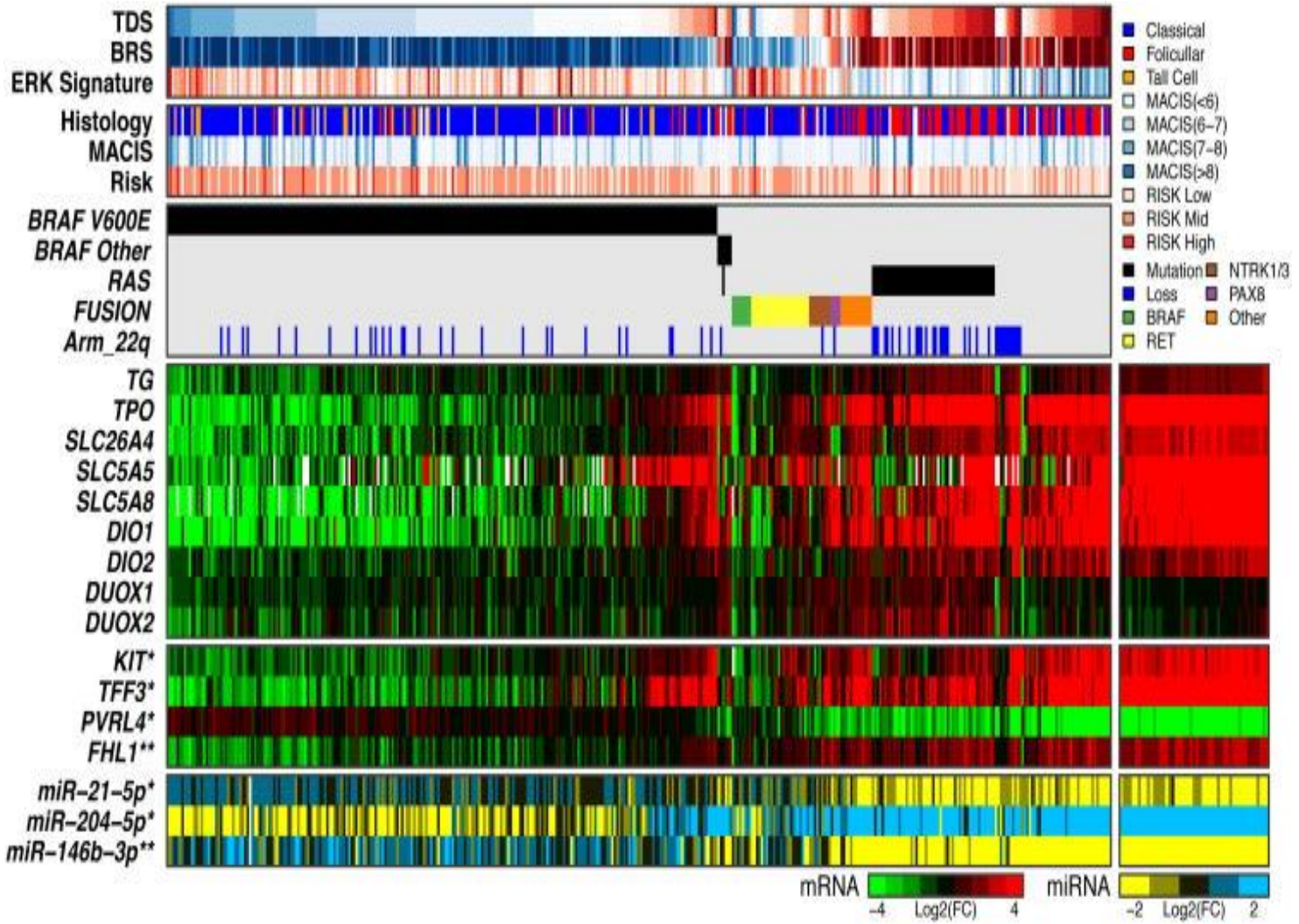


Summary

- Selumetinib enhances iodine incorporation in patients with RAI refractory thyroid cancer and reverses RAI resistance
- Selumetinib effects upon iodine incorporation may be dependent upon clinical factors (degree of residual iodine incorporation, FDG avidity, number of previous RAI treatments) and/or tumor genotype.
- Ho et al: N Engl J Med. 2013 Feb 14;368(7):623-32. doi: 10.1056/NEJMoa1209288

Thyroid Differentiation Score and Thyroid Cancers CGA

NIS



Pilot Study Summary

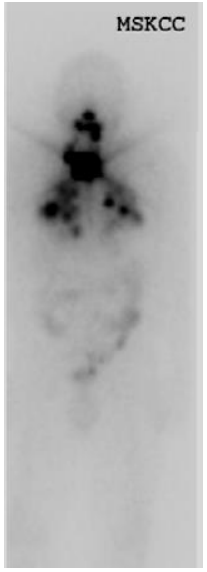
- The MEK inhibitor selumetinib can significantly enhance RAI incorporation/efficacy in a subset of RAIR thyroid tumors.
- RAS mutant patients may be particularly susceptible to this strategy.
- The impact of MEK inhibition upon RAI avidity in the *BRAF* MUT and *BRAF/RAS* WT cohorts was heterogeneous.

RAIR Disease: Restoring RAI Avidity

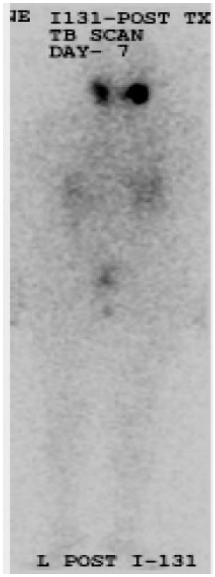
RECURRENT/METASTATIC DISEASE

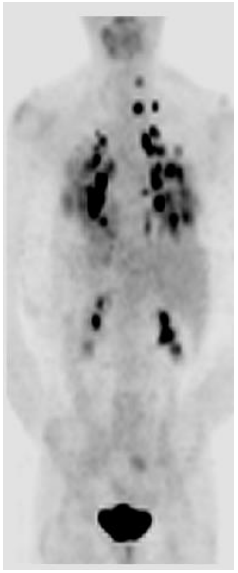
RAIA
(Curative or Palliative Intent)

RAIR
(Palliative Intent)



Strategies to restore RAI avidity?





^{131}I FDG