

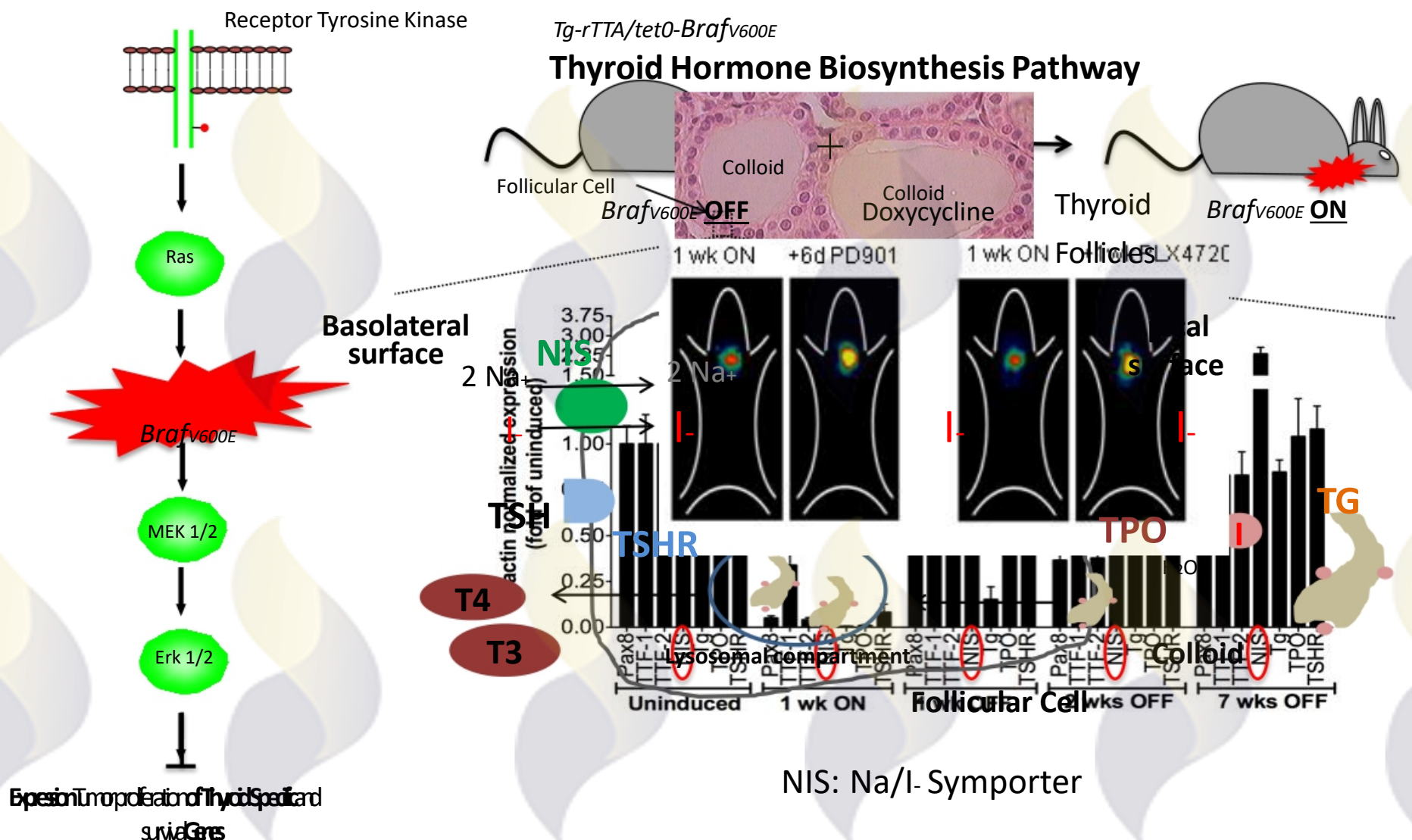
Redifferentiation Therapies for Thyroid Cancer

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Cancer Center™

Mitogen-Activated Protein Kinase (MAPK) pathway activation suppresses expression of NIS in thyroid cancer



Impact of selumetinib upon ^{124}I incorporation

N=20

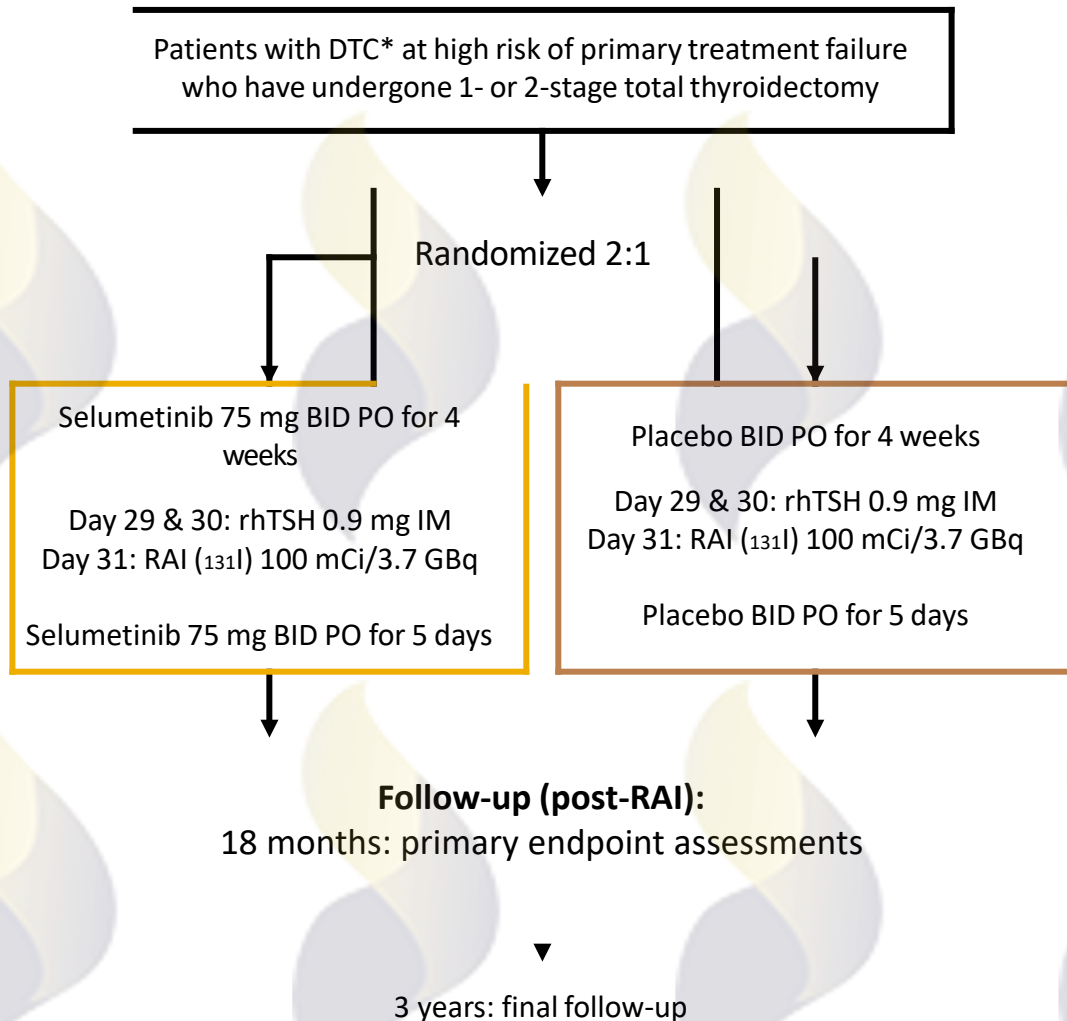
Patients with new/increased ^{124}I incorporation after selumetinib

12/20

Patients who went on to receive therapeutic RAI

8/12

ASTRA Phase III study



ASTRA was a Phase III, randomized, placebo-controlled double-blind study

Key inclusion criteria

- High risk of primary treatment failure:
 - Primary tumor >4 cm
 - Gross extrathyroidal extension outside the thyroid gland z(T4 disease)
 - N1a or N1b disease with ≥1 lymph node ≥1 cm
 - N1a or N1b disease involving ≥5 lymph nodes

Key exclusion criteria

- Patients with known distant metastasis

Primary endpoint

- Complete remission rate at 18-months
 - *For placebo and selumetinib, expected rates were 30% and 50%, respectively*

Secondary endpoints include

- Complete remission rate in patients with a *BRAF/NRAS* mutation at 18-months
- Clinical remission rate at 18-months
- Safety and tolerability

*Including papillary thyroid cancer, follicular thyroid cancer, and poorly differentiated thyroid cancer

BID, twice daily; DTC, differentiated thyroid cancer; IM, intramuscular; PO, orally; RAI, radioactive iodine; rhTSH, recombinant human thyroid stimulating hormone

Complete remission rate at 18 months (primary endpoint)

Group	Number (%) of patients with remission	Odds ratio	95% CI	2-sided p-value
Full analysis set (primary analysis)				
SEL + RAI (n=155)	62 (40.0)	1.07	0.61, 1.87	0.8205
PBO + RAI (n=78)	30 (38.5)			

Subgroup analyses of complete remission rate at 18 months

Group	Number (%) of patients with remission	Odds ratio	95% CI	2-sided p-value
<i>BRAF</i>-mutation positive				
SEL + RAI (n=84)	30 (35.7)	0.96	0.45, 2.12	0.9242
PBO + RAI (n=41)	15 (36.6)			
<i>BRAF</i>-mutation not detected				
SEL + RAI (n=54)	24 (44.4)	1.28	0.50, 3.40	0.6112
PBO + RAI (n=26)	10 (38.5)			

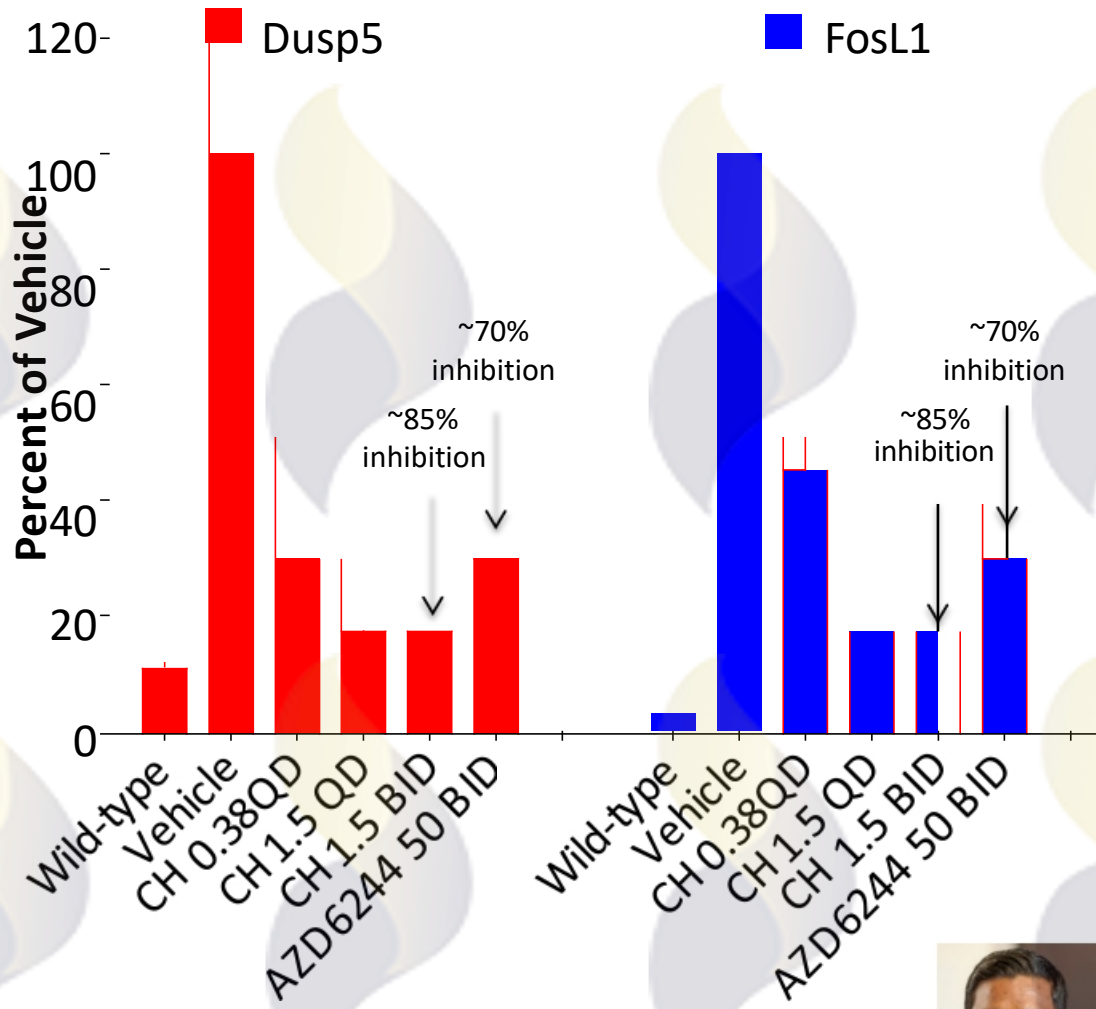
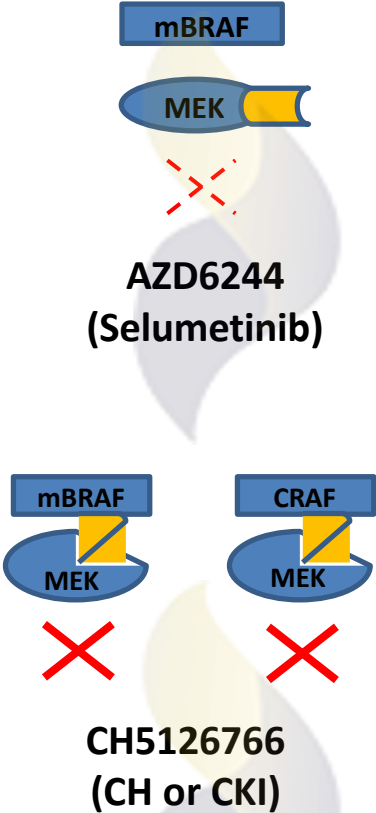
ASTRA Conclusions

- **Addition of selumetinib to RAI did not improve complete remission rate in this patient population at high risk of primary treatment failure**
- ASTRA was the first prospective study to evaluate the efficacy of adjuvant therapy for improving the complete remission rate in this patient population
- The placebo group established a 38.5% complete remission rate with standard RAI alone in high risk patients, suggesting the need for improved therapeutic approaches (predicted rate was 30% with placebo)
- The study was ambitiously designed to detect a 20% difference between placebo and selumetinib
- ~~Subgroup analyses suggest~~ that treatment compliance and tailoring the targeted therapy approach to the oncogenic driver mutation may be critical design elements to consider for future trials

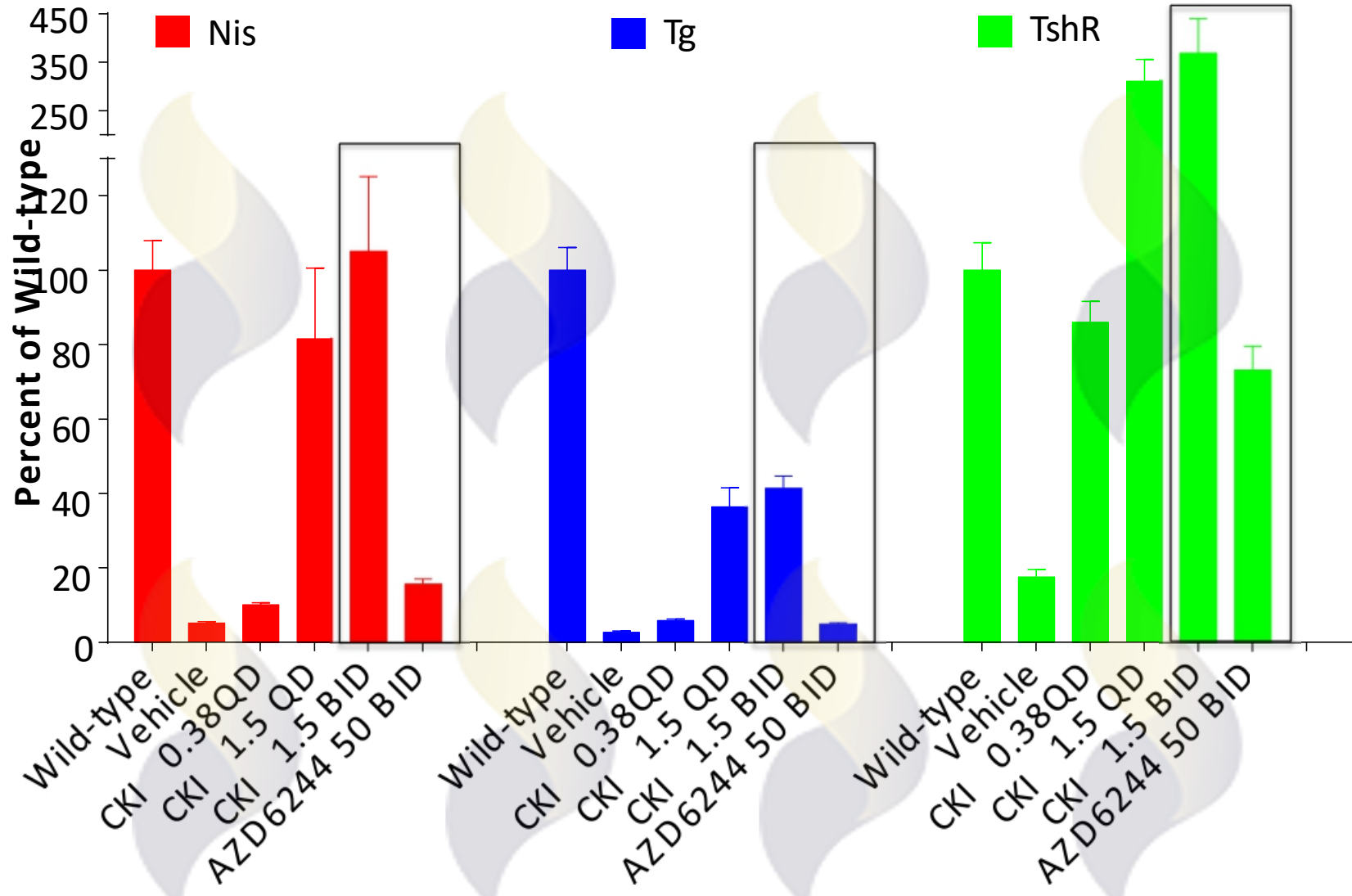
Ho A et al. J Clin Oncol 2022

Modest differences in MAPK pathway inhibition....

TPO-Cre LSL-BRAF^{V600E} PTC mouse model
 (4.5 days of drug treatment)

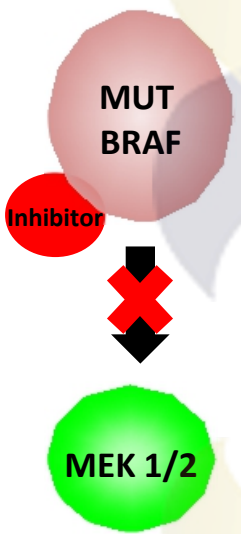


... translate to significant changes in iodine metabolism gene expression

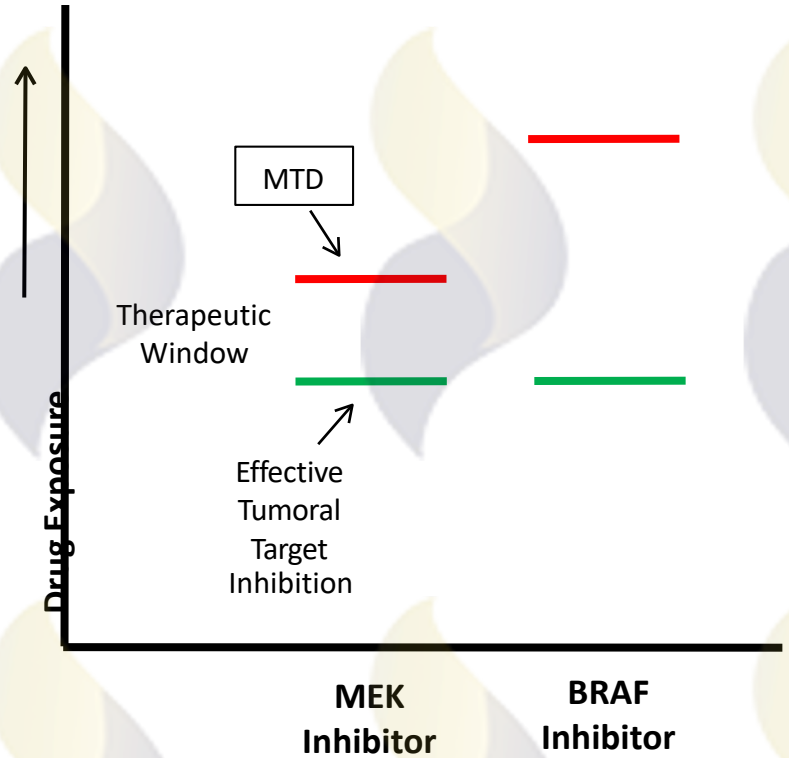
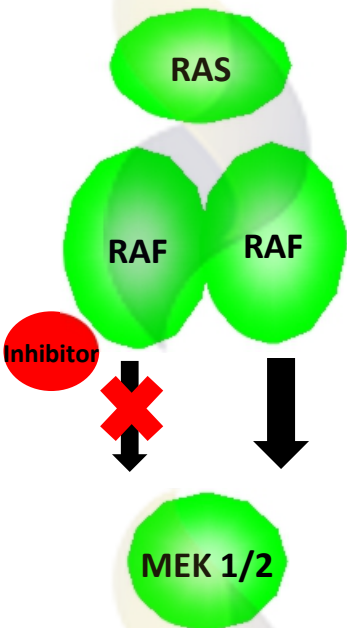


BRAF MUT Tumors: Alternatives to MEK Inhibition

BRAF Mutant Cell (Tumor)

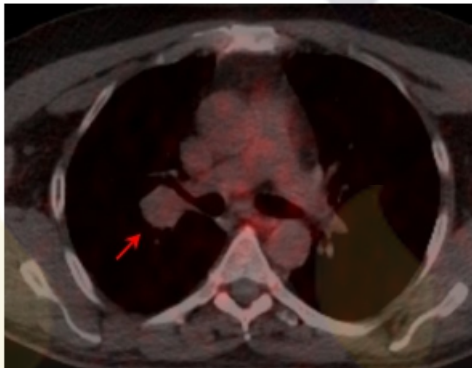


BRAF WT Cells (Normal Tissues)

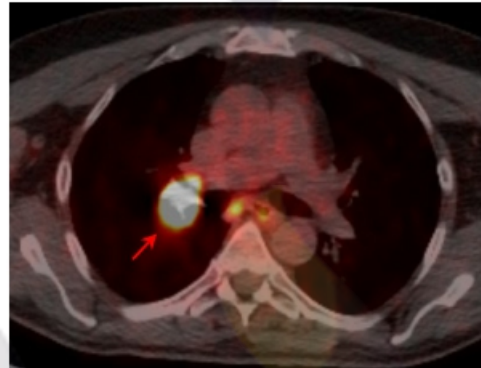


Poulikakos, *Cancer Cell*, 19: 11-15, 2011
 Poulikakos et al., *Nature*, 18:427-431, 2010

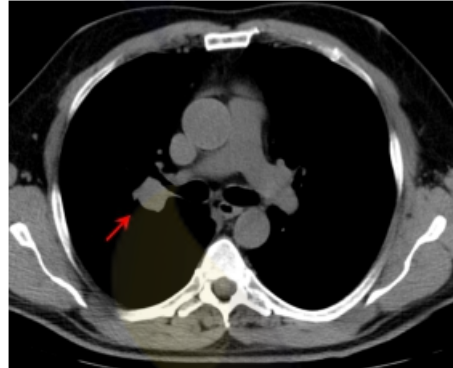
Pilot Study of Vemurafenib plus RAI for RAIR, BRAF MUT Disease



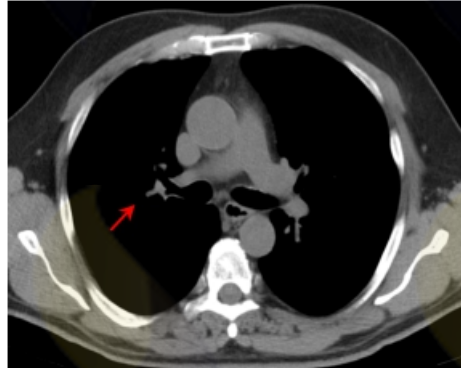
Baseline



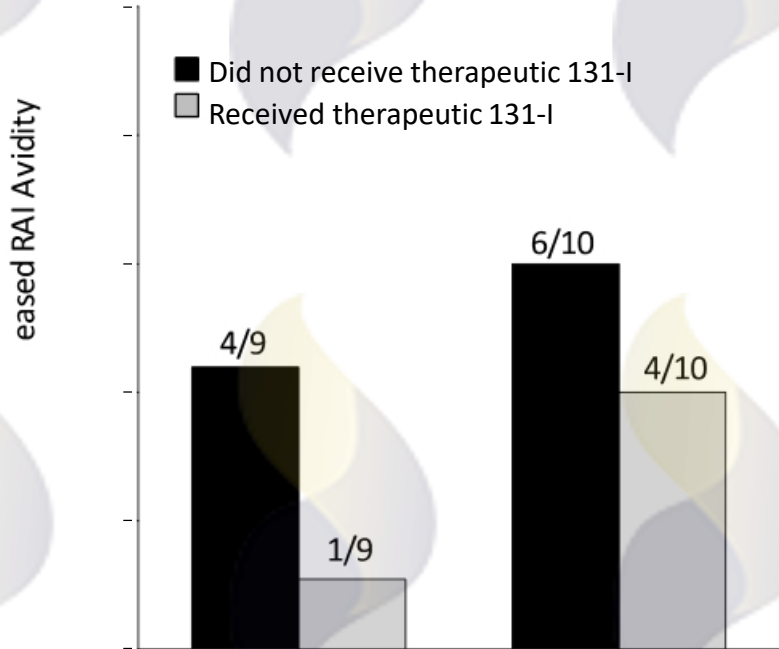
Post-vemurafenib (~4 wks)



Baseline



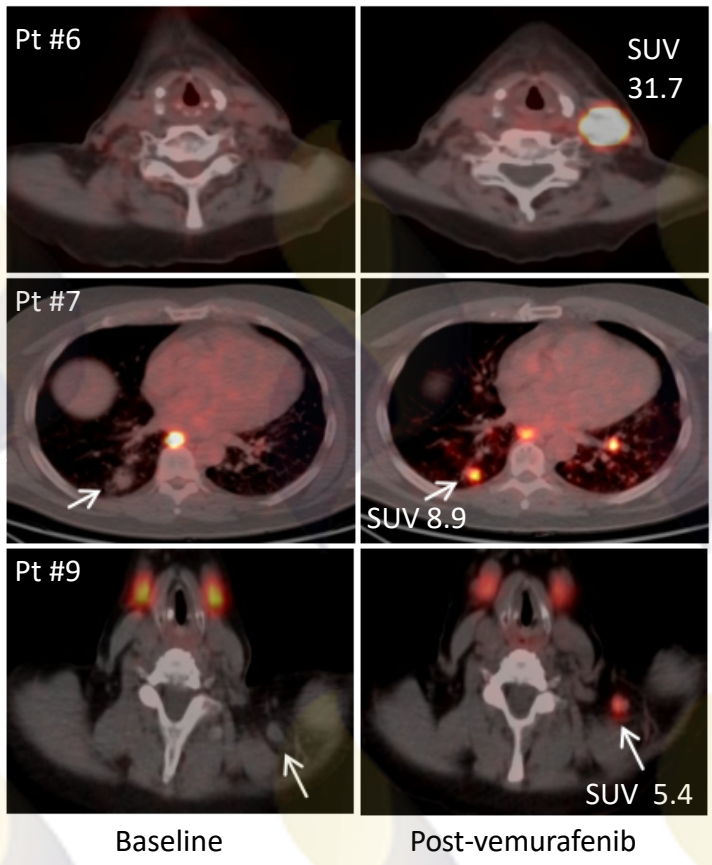
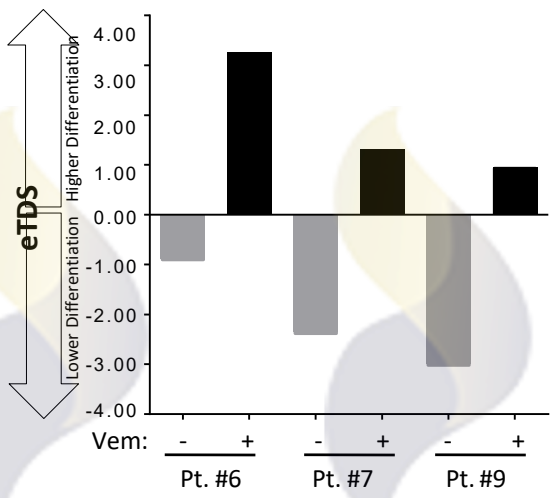
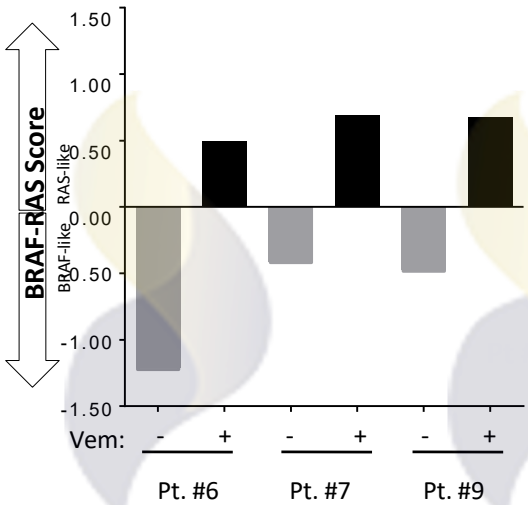
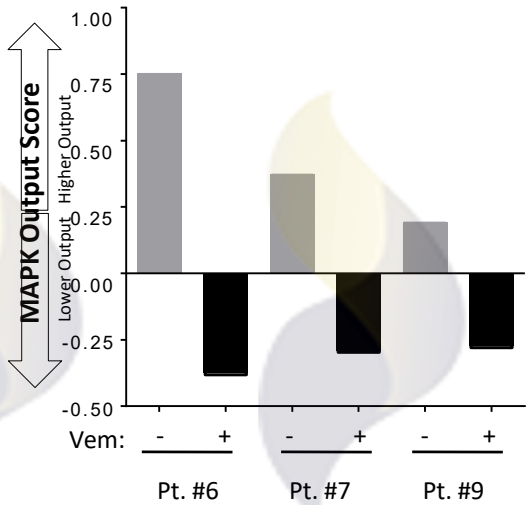
6 mos s/p vemurafenib + RAI



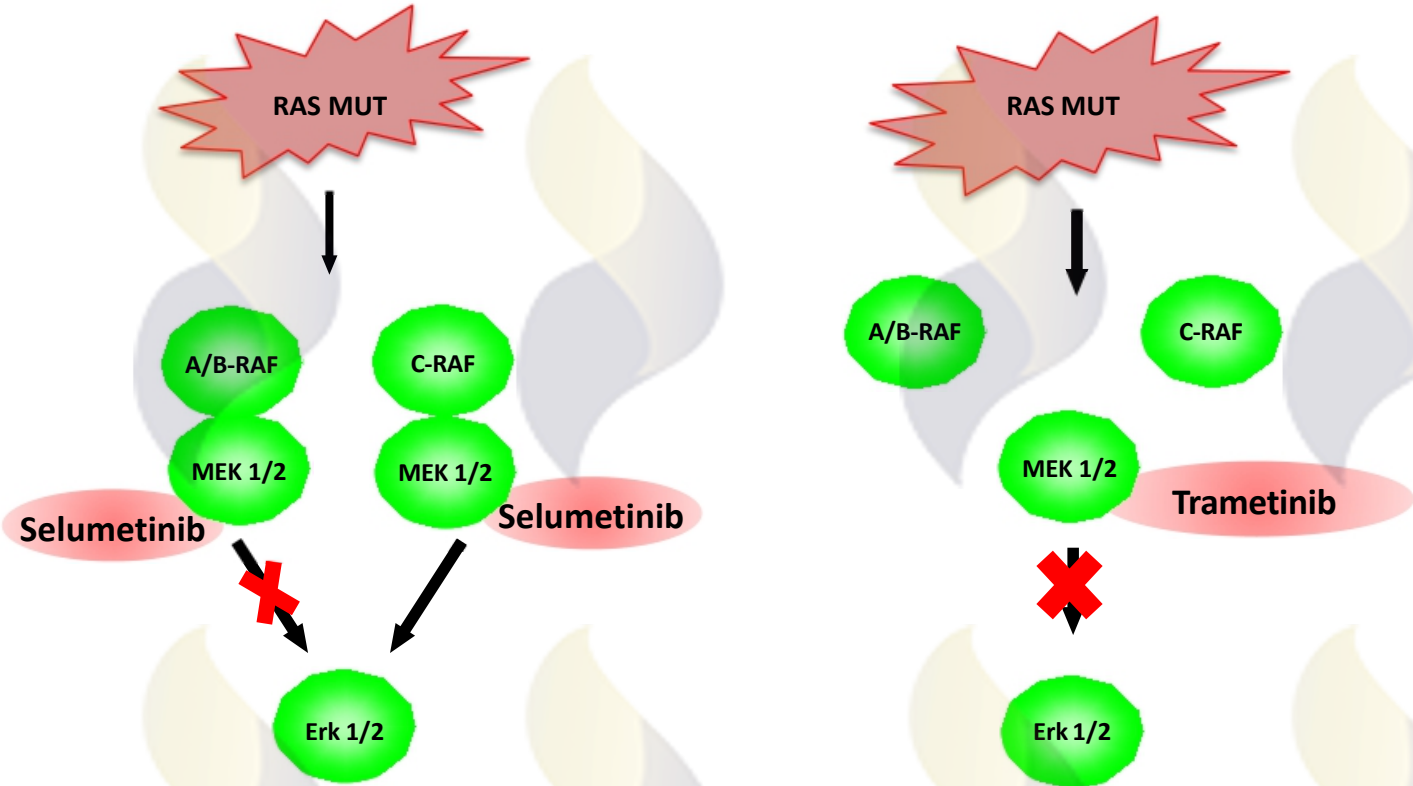
	RECIST Response Outcomes (PR+SD)
Selumetinib	1/9 (1 PR)
Vemurafenib	4/10 (2 PR, 2 SD)



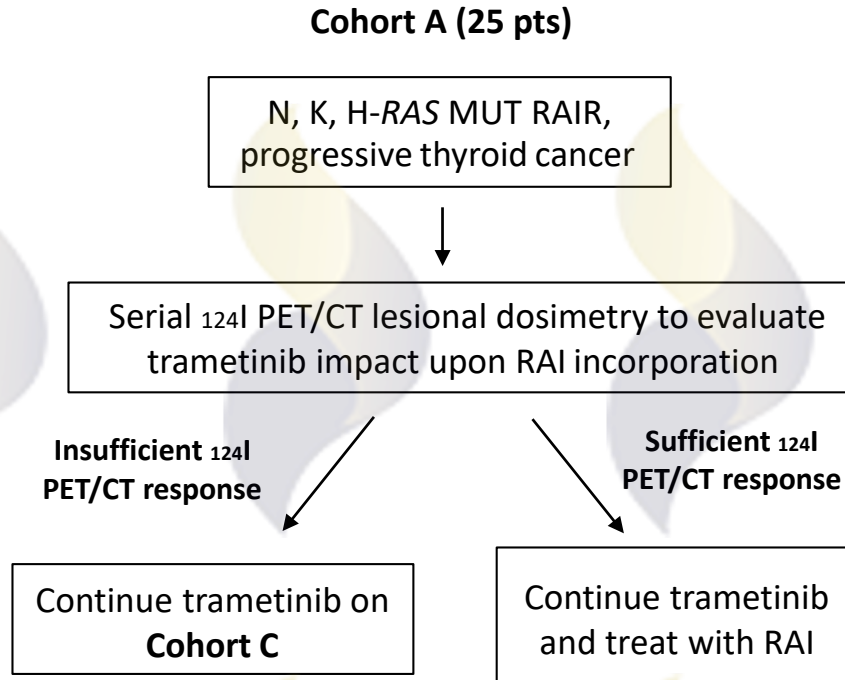
MAPK Output, Thyroid Differentiation, and I-124 Avidity with Vemurafenib



Not All MEK Inhibitors Are Created Equal



Phase II of MEK Inhibition (Trametinib) plus RAI in RAI-R, Thyroid Cancers (*RAS* Mutant)



Primary Objectives (Cohort A): Evaluate PFS at 6 months and overall response at 6 months

Cohort : RAS Mutant RAI R DTC

n=25

Patients with new/increased ¹²⁴I incorporation after trametinib

22/25 (88%)

Patients who were eligible for therapeutic RAI

15/25 (60%)

RECIST Response @ 6 mos

n=14 received RAI

Partial Responses

8 (32%) (57% of RAI pts)

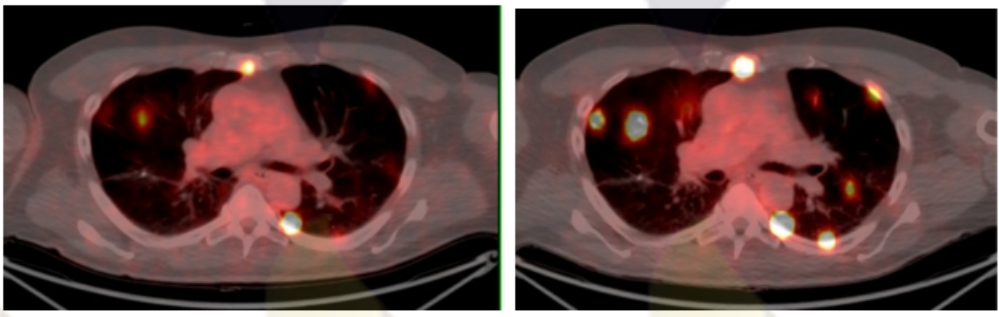
Clinical Benefit (PR+SD@6 mos)

12 (48%) (86% of RAI pts)

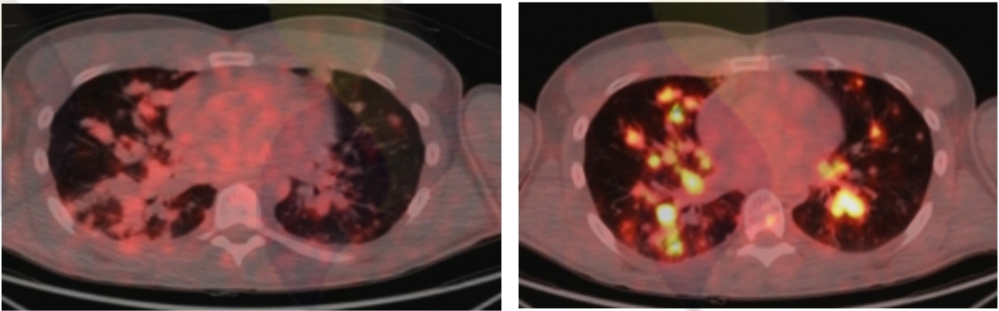
Progressive Disease

2 (8%) (14% of RAI pts)

Patient A



Patient B

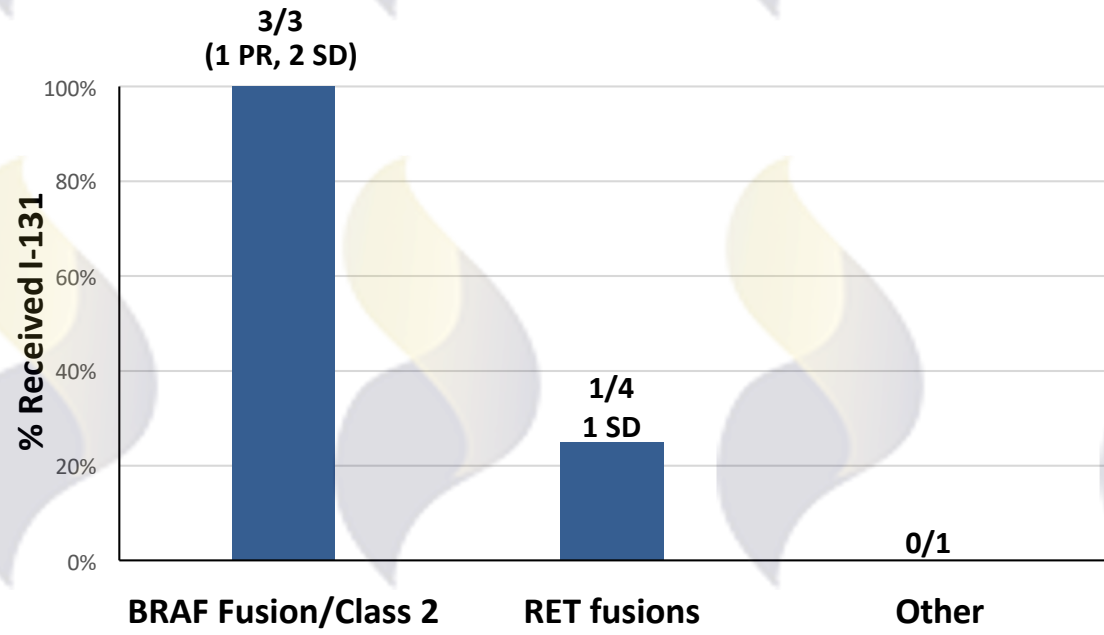


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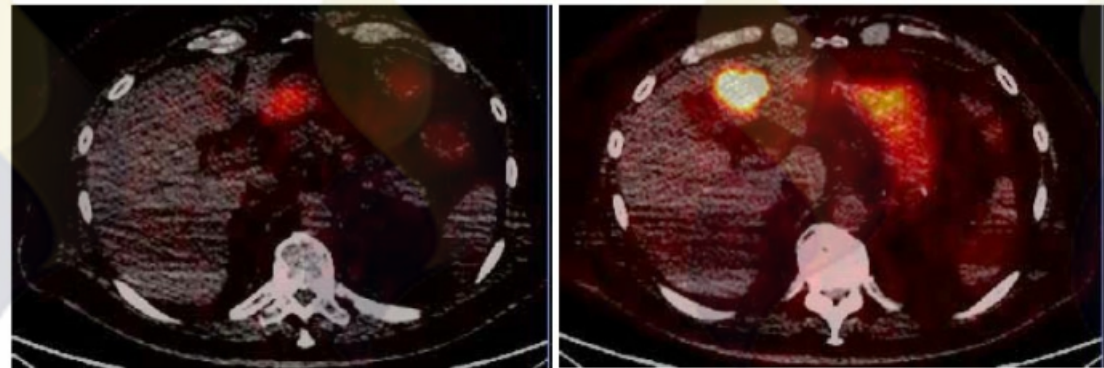
Baseline

Post-Trametinib

Cohort B: RAS WT/non-V600 BRAF (n=9)



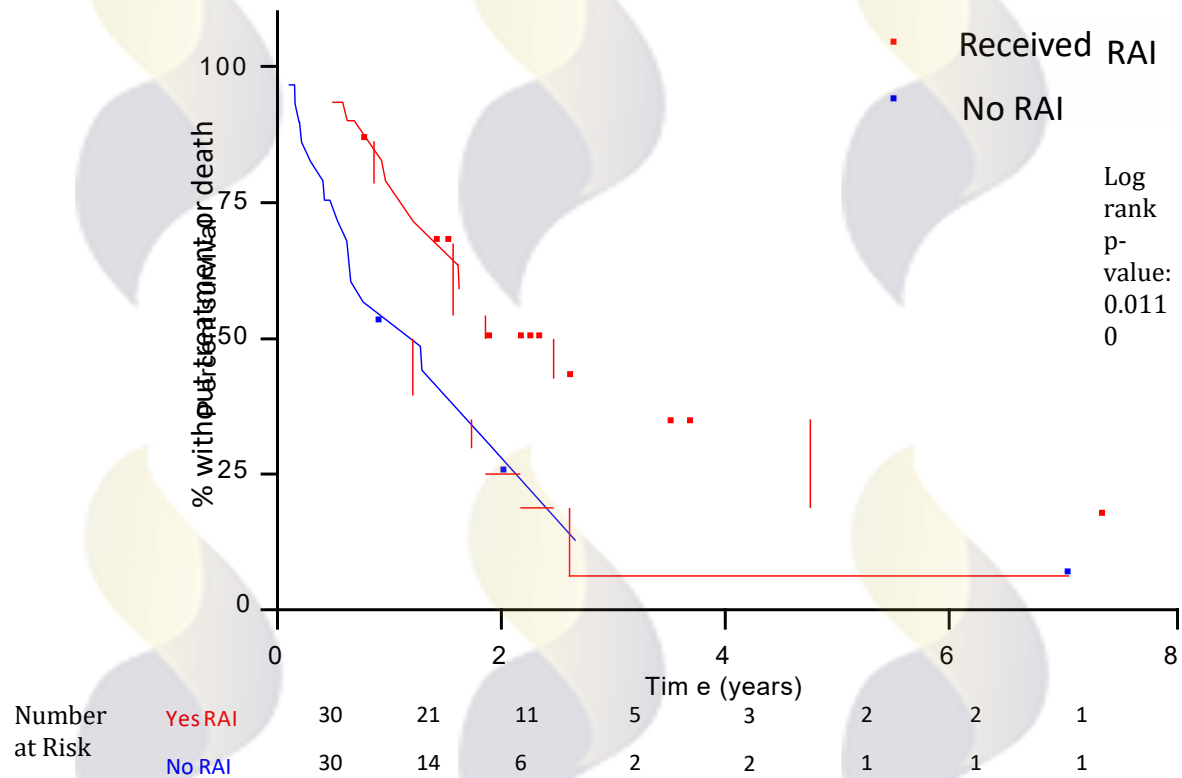
PRKAR2B-BRAF (PR; -69% regression)



Cumulative Redifferentiation Experience for RAI Disease (n=69)

69 RAI patients treated on a redifferentiation trial
34 (49%) received I-131
18 PRs, 12 SD @ 6-mos after I-131

Time to Subsequent Therapy or Death



Efficacy of the phase 2 redifferentiation trials

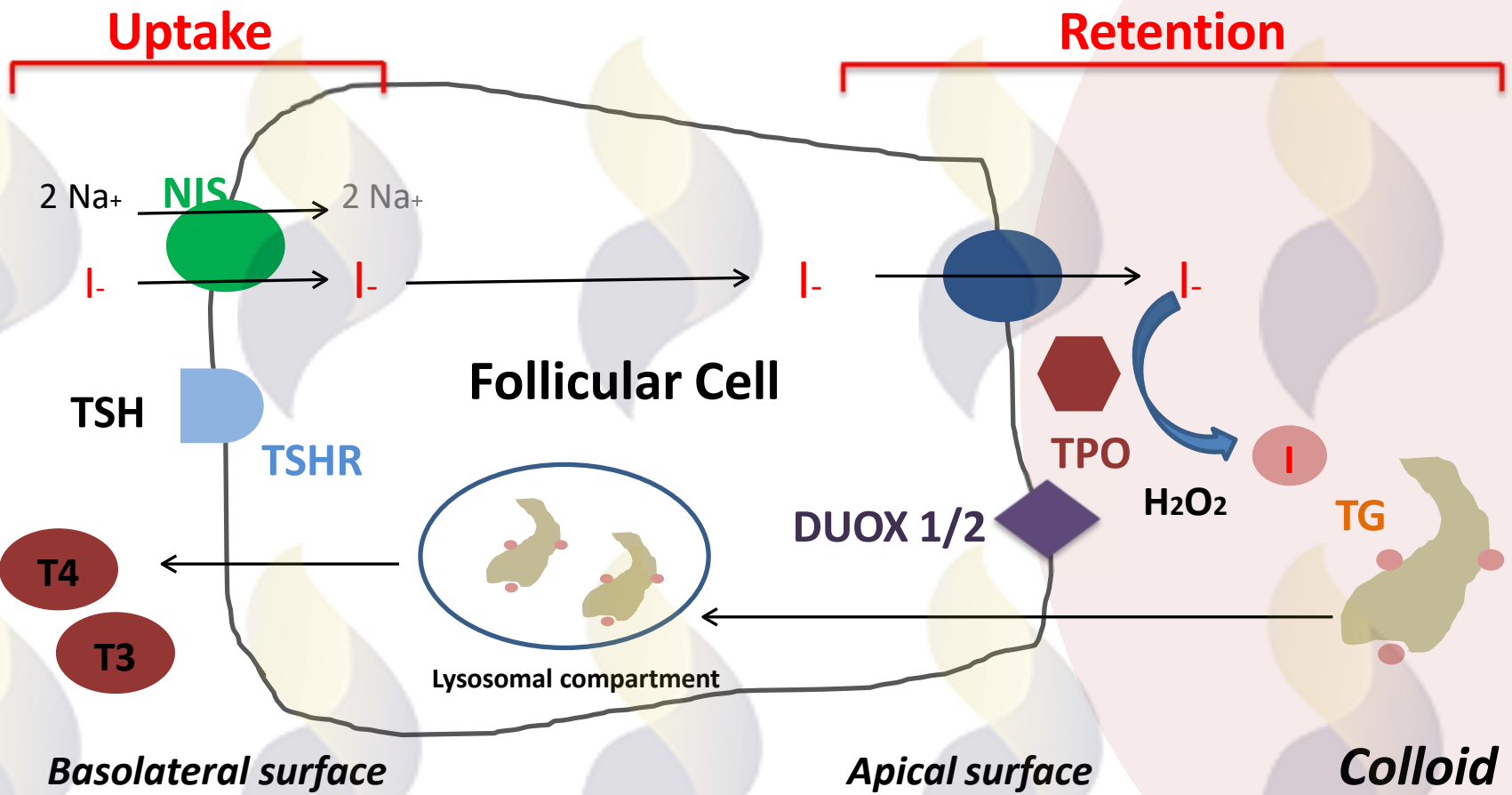
	Drug	n	Genotype	Increase of RAI uptake	Rx with RAI (n)	CR	PR	PFS
Ho, 2012	Selumetinib +/- 131I	20	BRAF V600E RAS & other	12 (60%) 124I PET/CT	8 (dosimetry, ≥ 20Gy)	0	25 % (5) (best PR)	-
Rothenberg 2015	Dabrafenib +/- 131I	10	BRAF V600E	6 (60%) Dc 131I WBS	6	0	20 (2) (best PR)	-
Dunn, 2018	Vemurafenib +/- 131I	12	BRAF V600E	4 (40%) Dc 131I WBS	4	0	25% (4) (best PR)	- *
Leboulleux, 2021	Dabrafenib + Trametinib + 131I	21	BRAF V600E	95% (20) Post T WBS	21	0	38% (8) (6 months PR)	- **
Leboulleux, 2021	Trametinib + 131I	10	RAS	60% (6) Post T WBS	10	0	20% (2) (6 months PR)	-

* : Time to other treatment in the responder : 9, 18, 32 and > 19 months

** : Follow-up 18-36 months planned in the protocol;

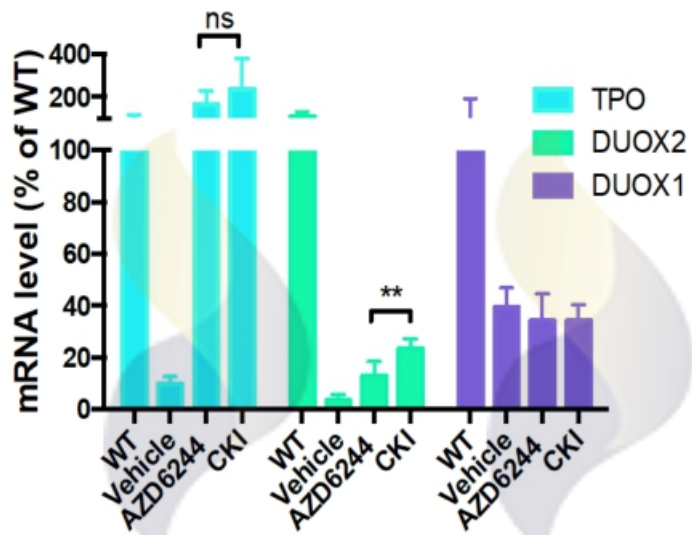
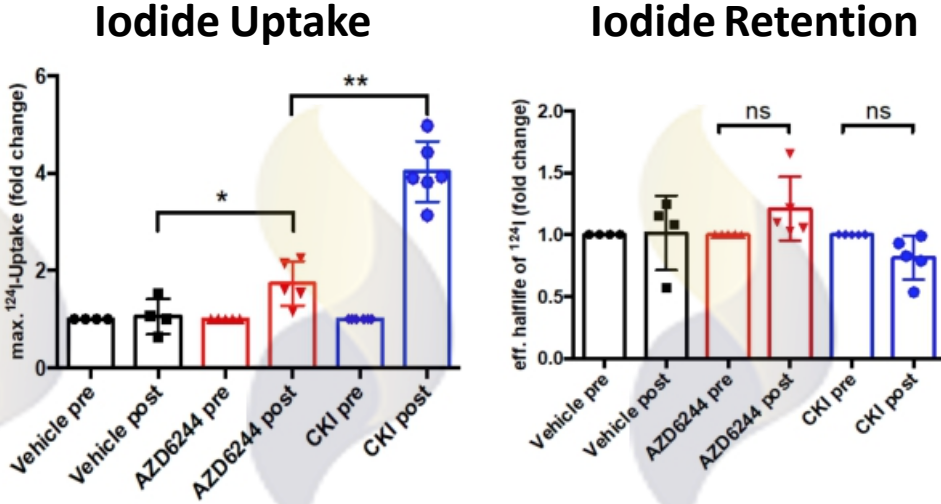
“8 patients still in PR, median duration of response : 13.2 months, range [6.0 ; 25.9] »

Thyroid Hormone Biosynthesis



MAPK Inhibition in *BRAF* Mutant Mouse Models Do Not Impact Iodide Retention

TPO-Cre LSL-BRAF^{V600E} PTC mouse model



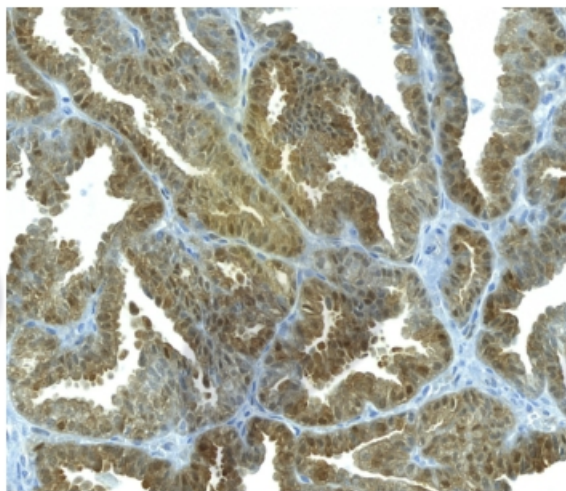
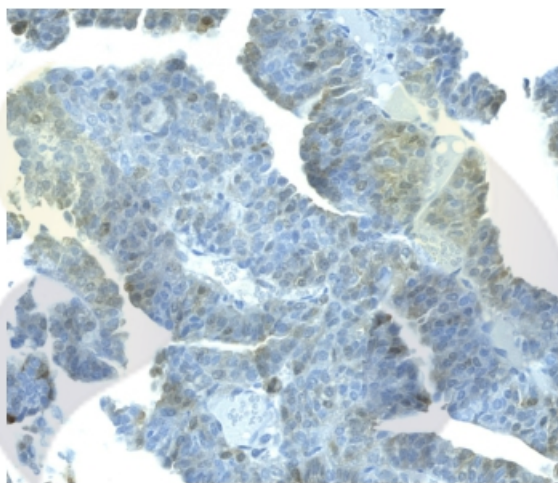
Combined BRAF-MEK Inhibition Increases Akt Phosphorylation

TPO-Cre LSL-BRAF^{V600E} PTC mouse model

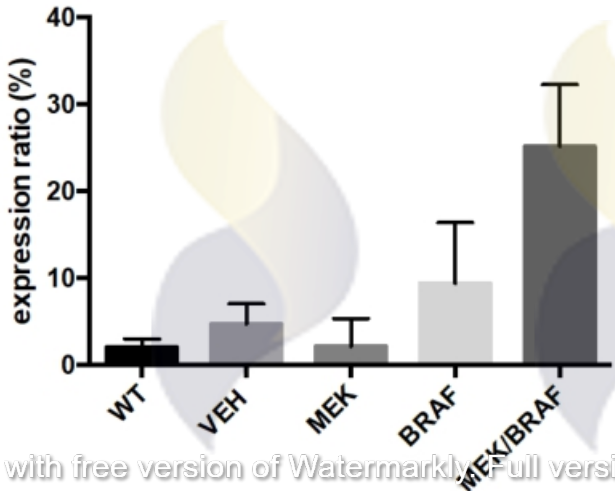
Vehicle

LGX818 + MEK162

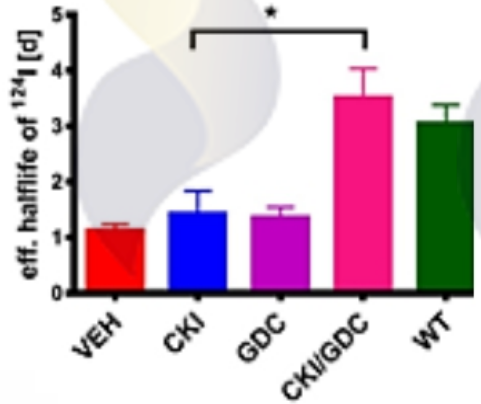
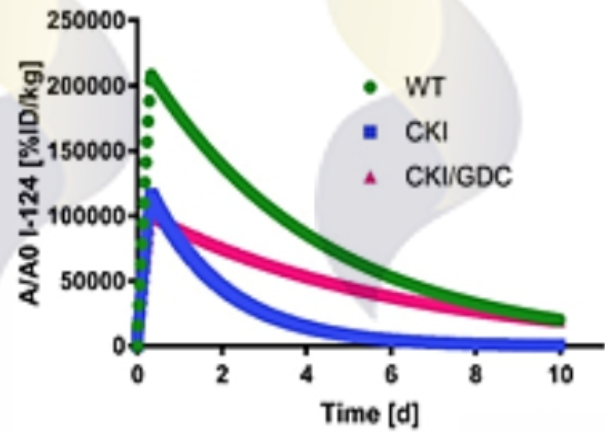
pS308-AKT



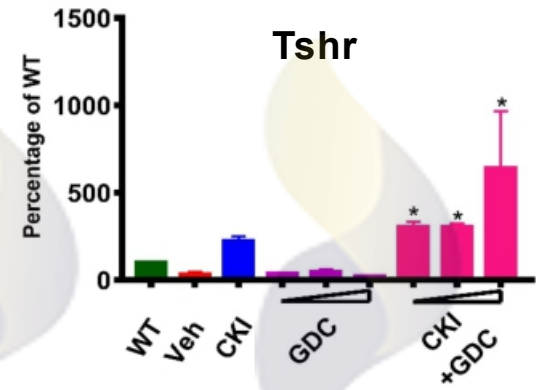
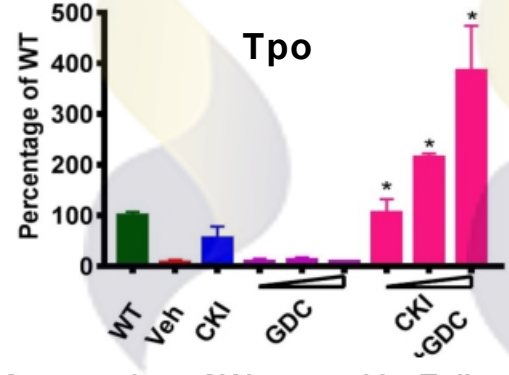
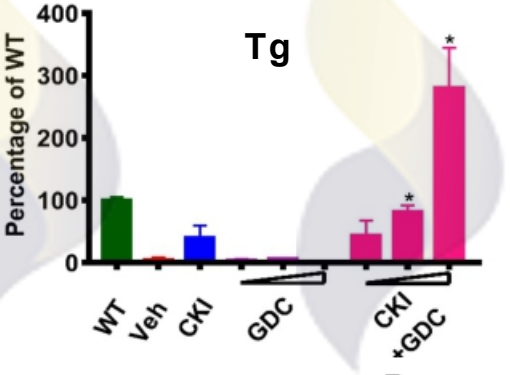
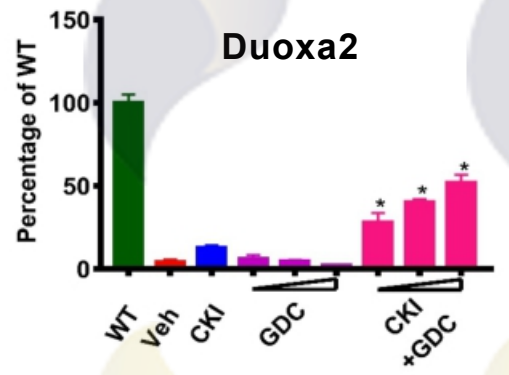
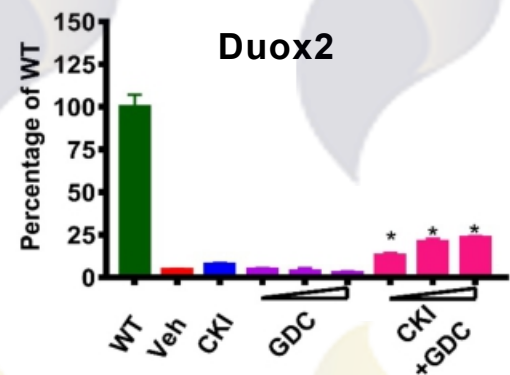
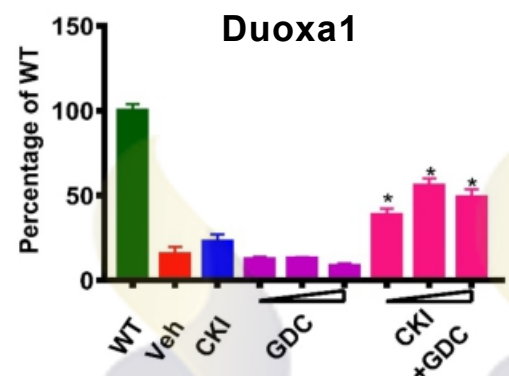
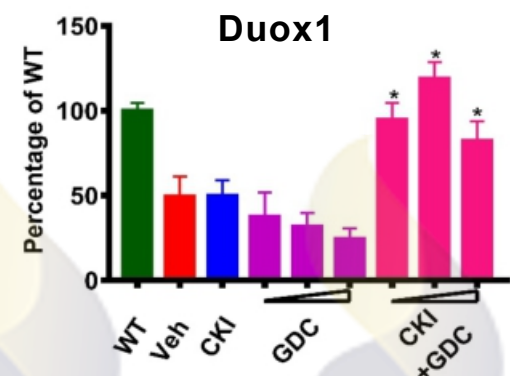
pAKT



CKI + pan-class I PI3K inhibitor pictilisib (GDC0941) x 1 wk impact on ¹²⁴I uptake and retention in PTC of *LSL-Braf^{V600E}* mice



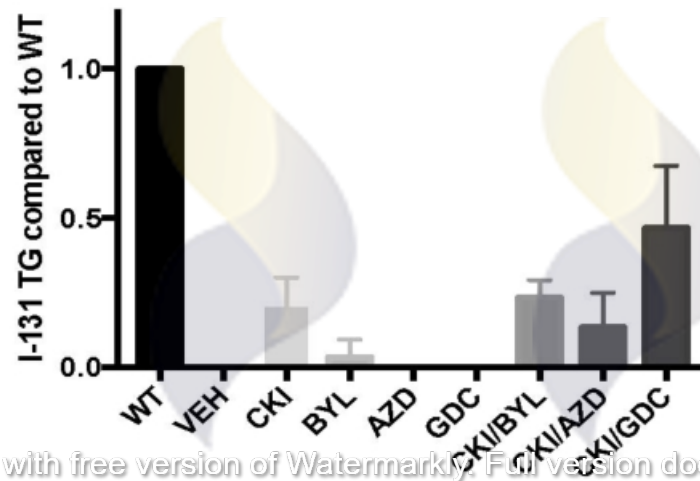
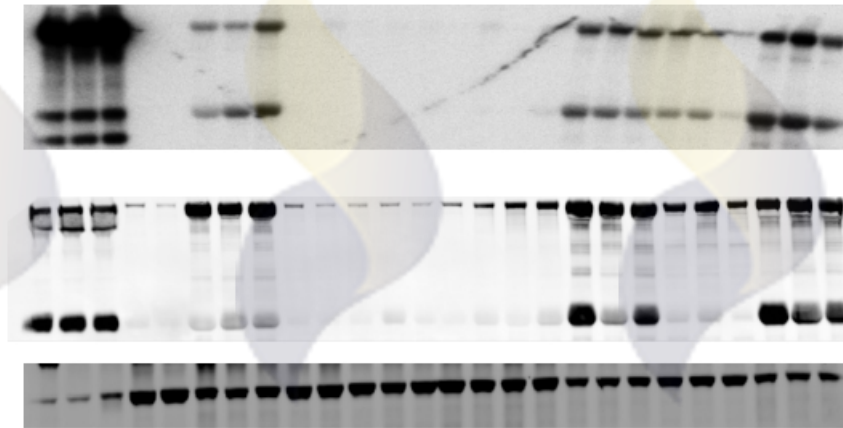
Duox1/2 Upregulation with Dual MAPK/PI3K Inhibition



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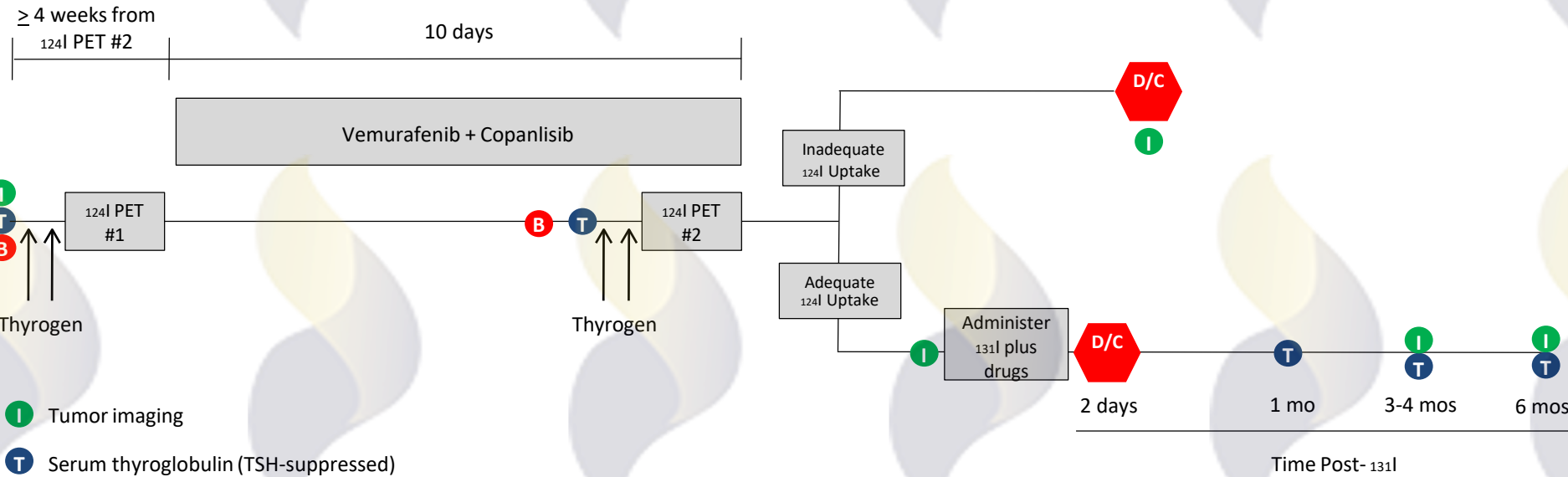
Effects of selective MAPK and/or PI3K pathway inhibitors on iodine incorporation into Tg

¹³¹I-Tg post 72h Rx: WT Veh CKI BYL AZD GDC CKI/ CKI/ CKI/
BYL AZD GDC



BYL: BYL719
 AZD: AZD6482
 GDC: GDC0941

Phase I Trial of Vemurafenib plus the Pan-PI3K Inhibitor Copanlisib (Bayer)



- I Tumor imaging
- T Serum thyroglobulin (TSH-suppressed)
- B Serial research biopsies at baseline and Week 3
- D/C Discontinue vemurafenib and copanlisib

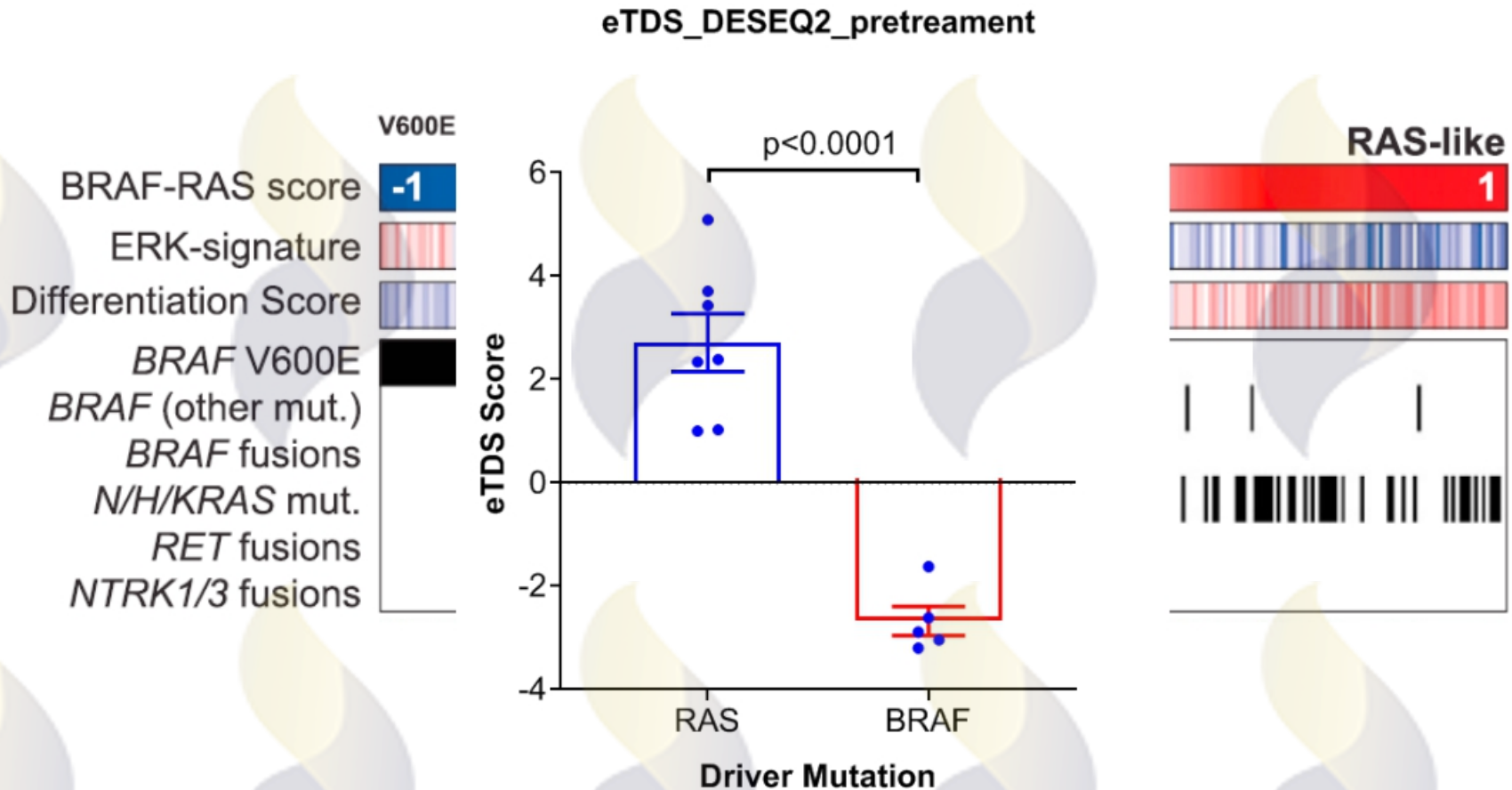
Primary Objective: To identify the maximum tolerated dose (MTD) of vemurafenib plus copanlisib for *BRAF* mutant, RAIR thyroid cancer patients.

Secondary Objectives: Enhancement of RAI avidity, receive RAI treatment, impact on I-124 uptake versus retention, ORR/PFS with RAI therapy.

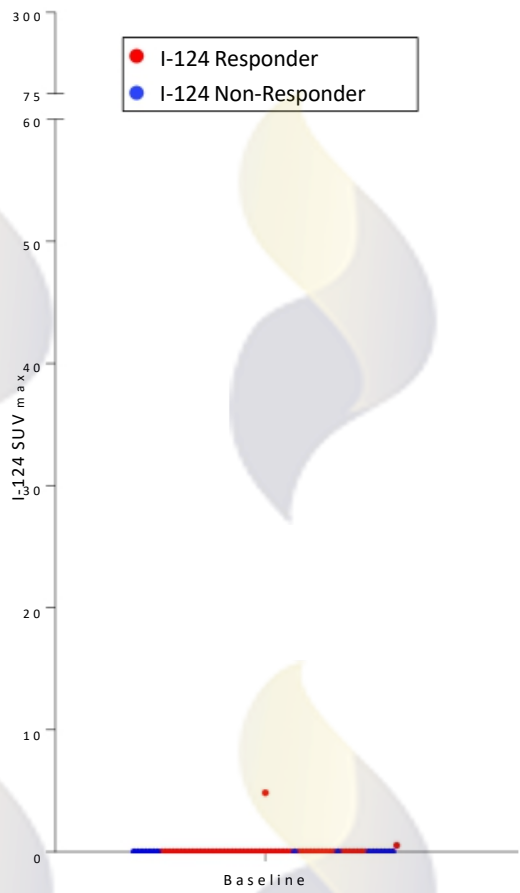
Exploratory Objectives: Impact upon thyroid specific gene expression and MAPK/PI3K output

Dose Level	Vemurafenib Dose	Copanlisib Dose
-2	480 mg PO bid	45 mg IV weekly
-1B	720 mg PO bid	60 mg IV weekly
-1A	720 mg PO bid	45 mg IV weekly
1	960 mg PO bid	45 mg IV weekly
2	960 mg PO bid	60 mg IV weekly

TCGA: Spectrum of thyroid-specific gene expression

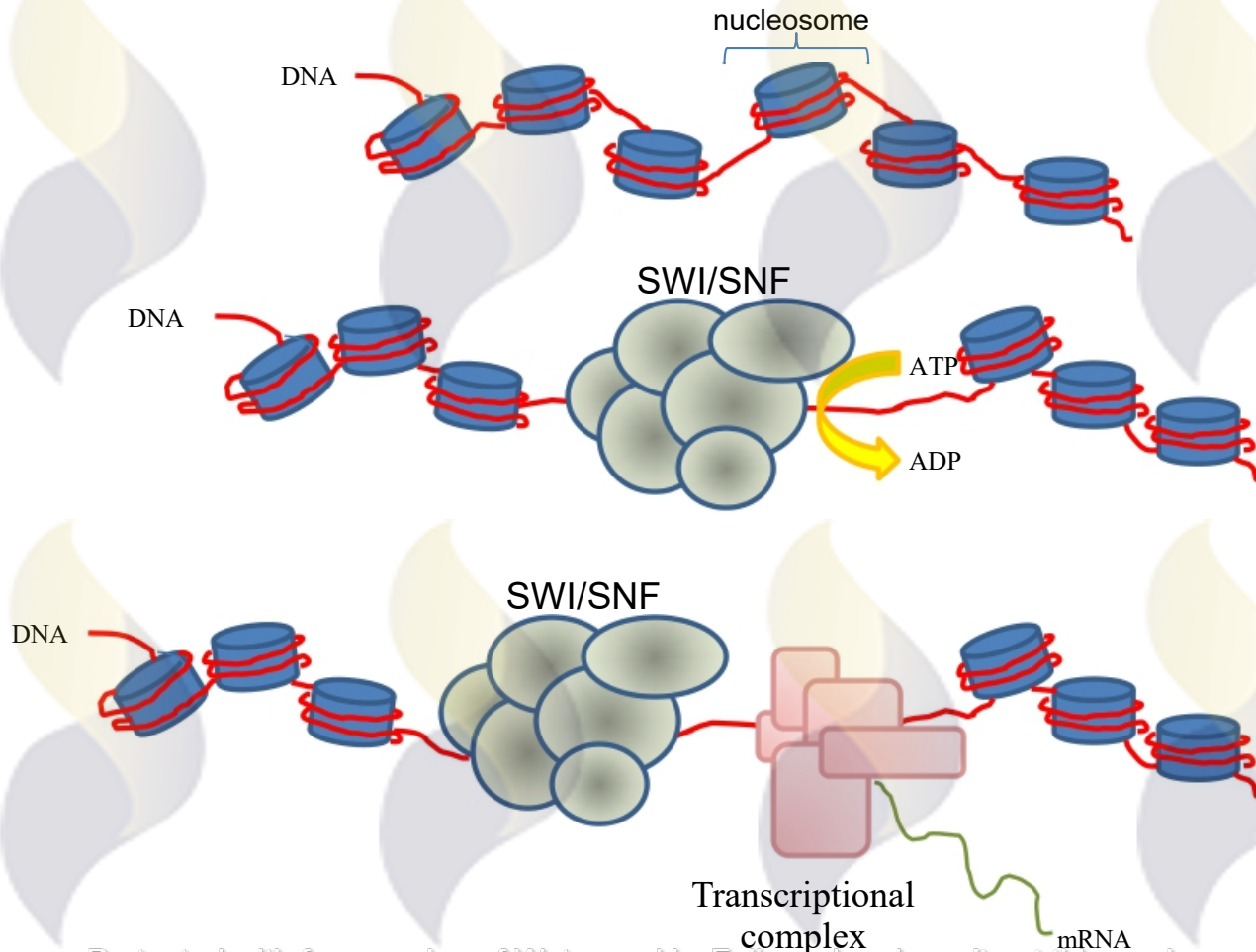


Baseline TG as Marker of Differentiation: Vemurafenib Redifferentiation



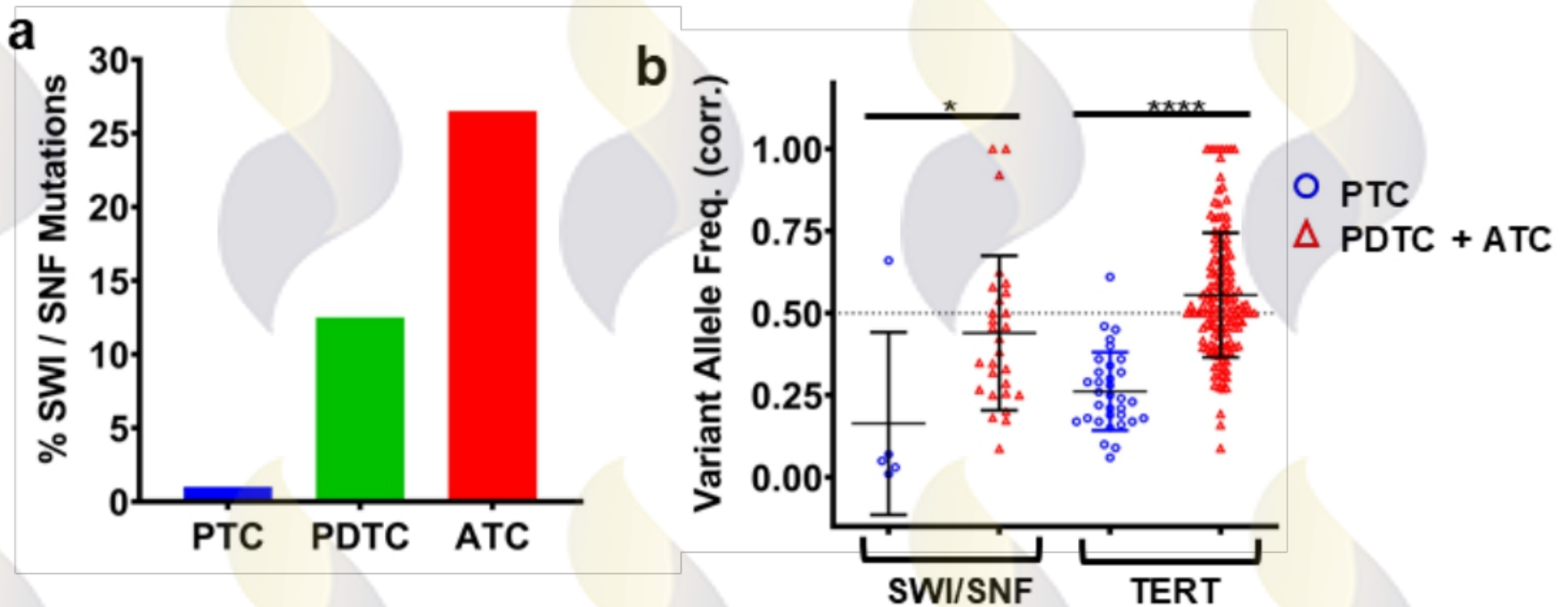
SWI/SNF Complexes

Evolutionarily conserved multisubunit complexes that utilize the energy of ATP hydrolysis to mobilize nucleosomes and remodel chromatin.

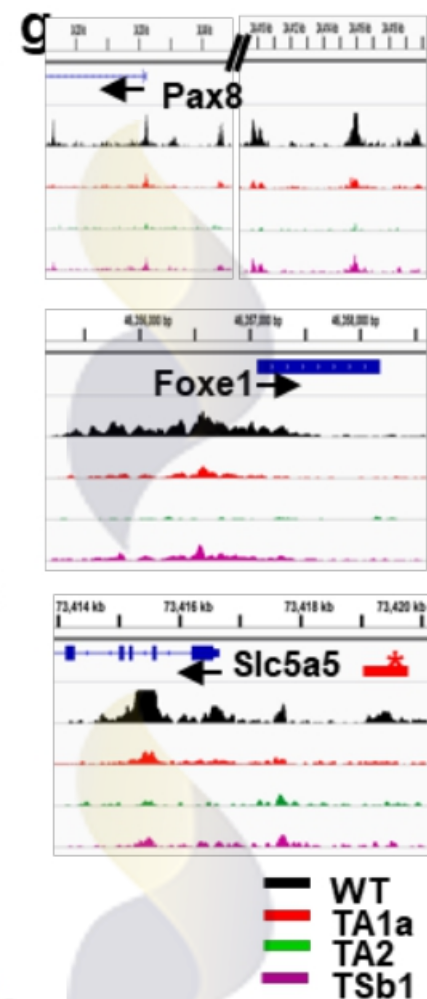
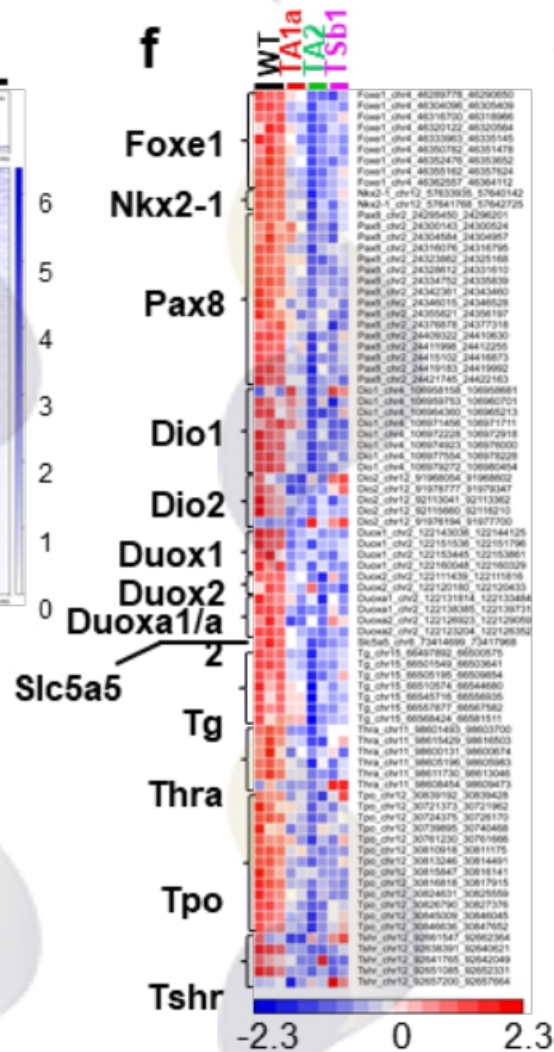
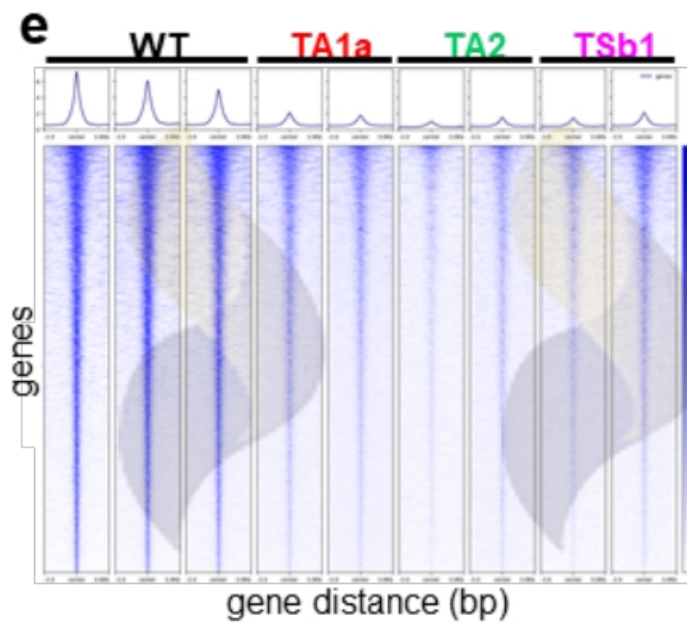


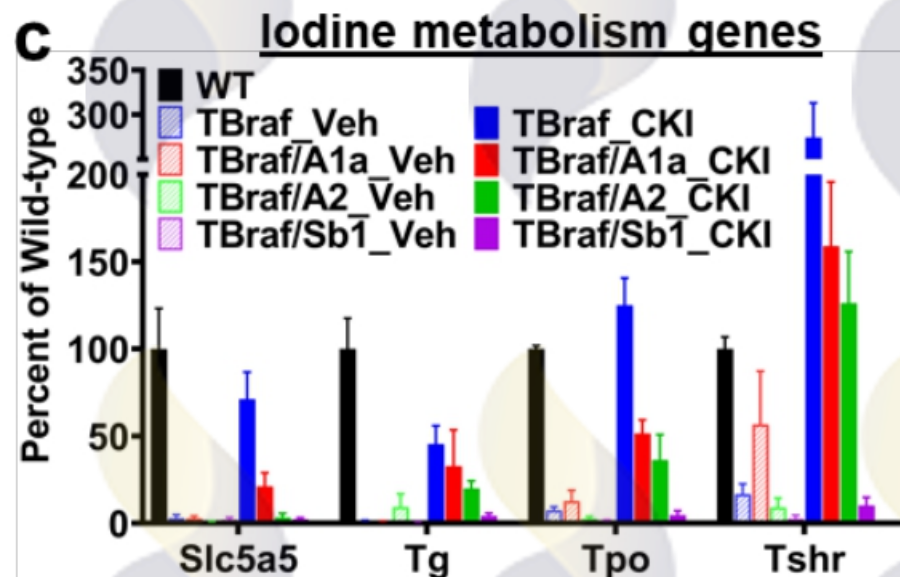
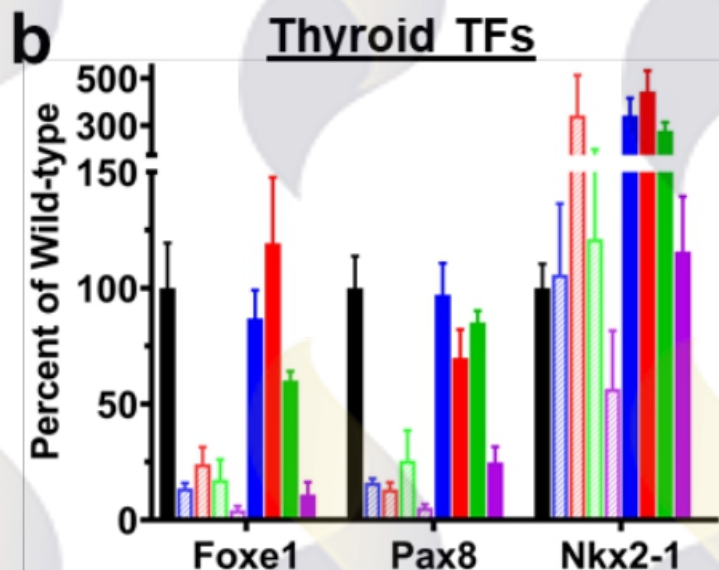
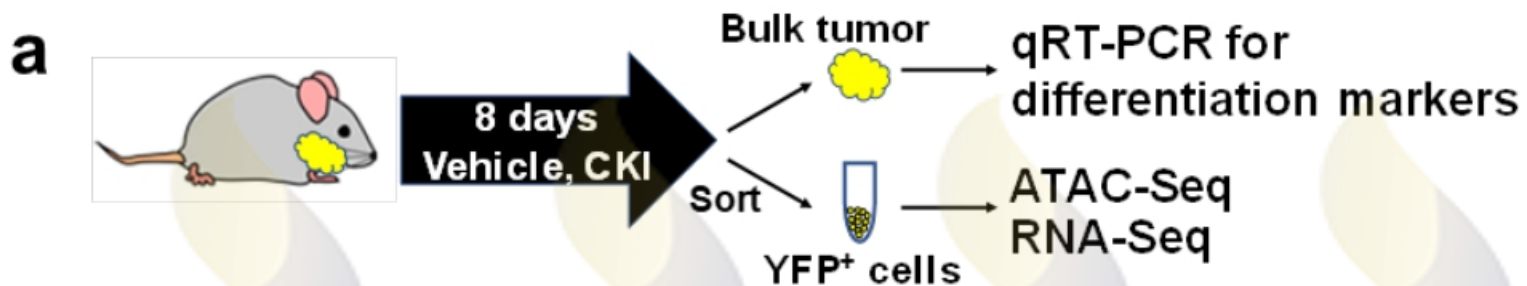
SWI/SNF mutations in thyroid cancer

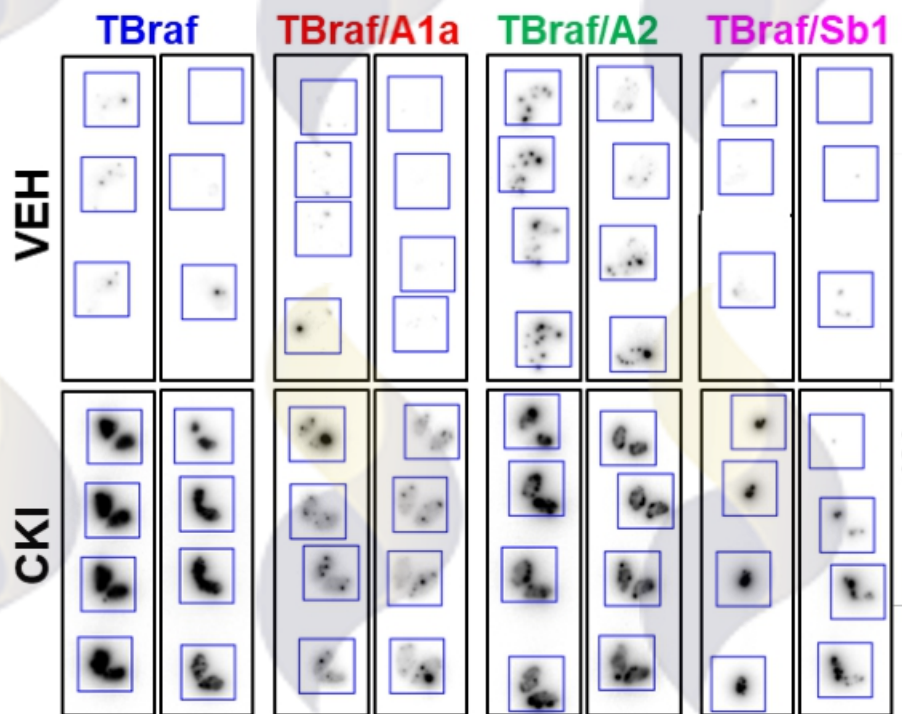
Multisubunit complexes that mobilize nucleosomes and remodel chromatin.



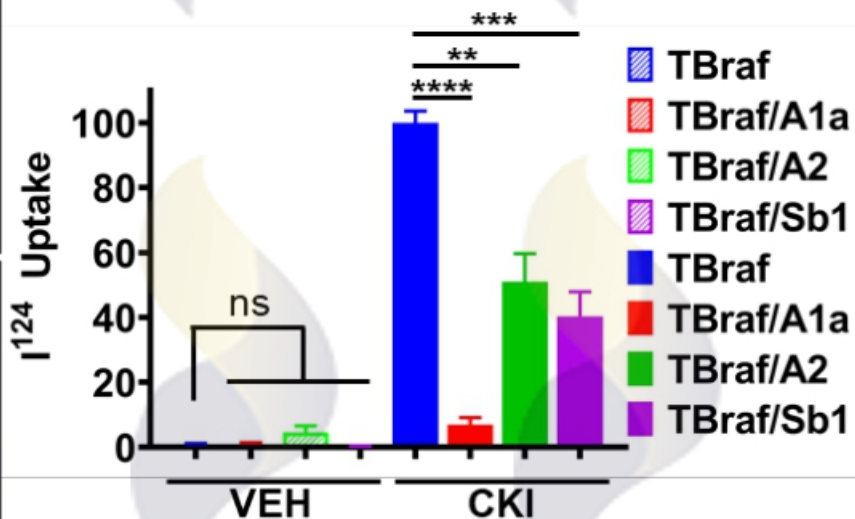
Landa I. J Clin Invest 2016.



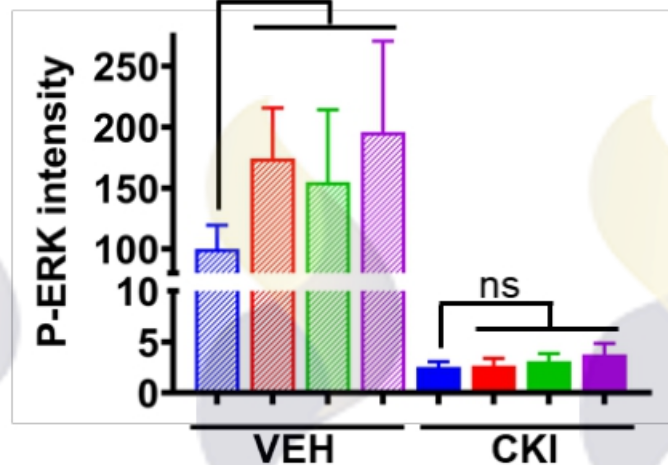




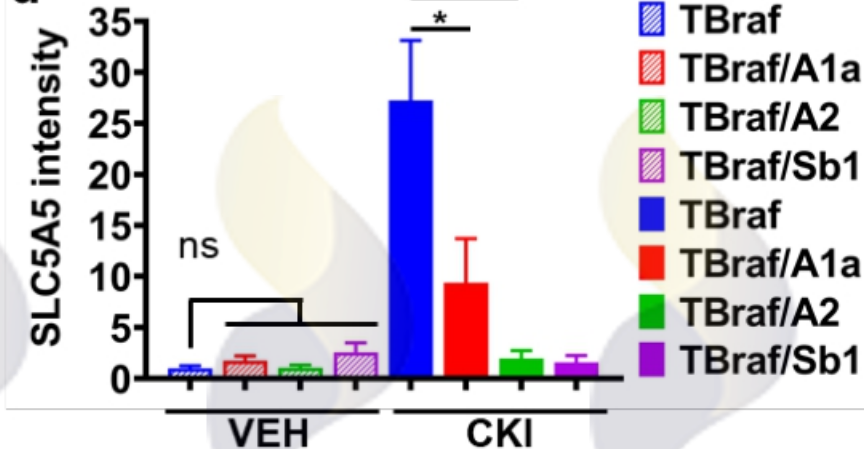
b



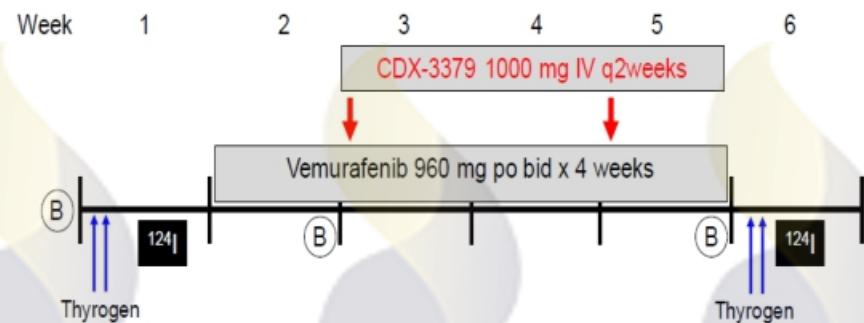
c



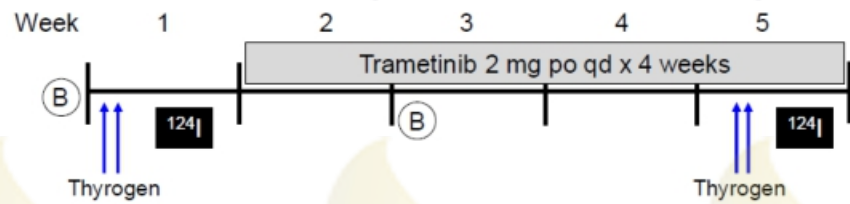
d



NCT02456701



NCT02152995



25 patients

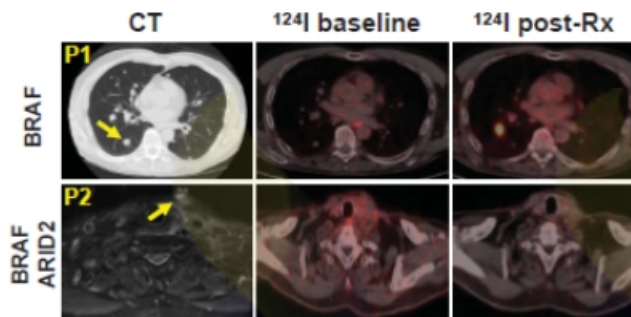
Responders

0/15 with A1a, A2 or Sb1 alterations

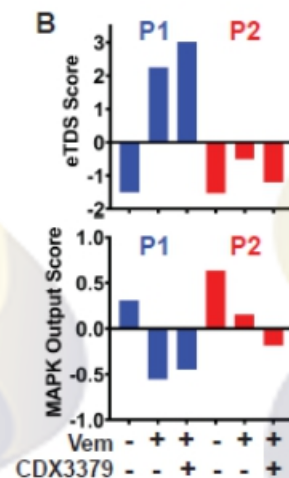
Non-responders

3/10 with A1a, A2, or Sb1 alterations

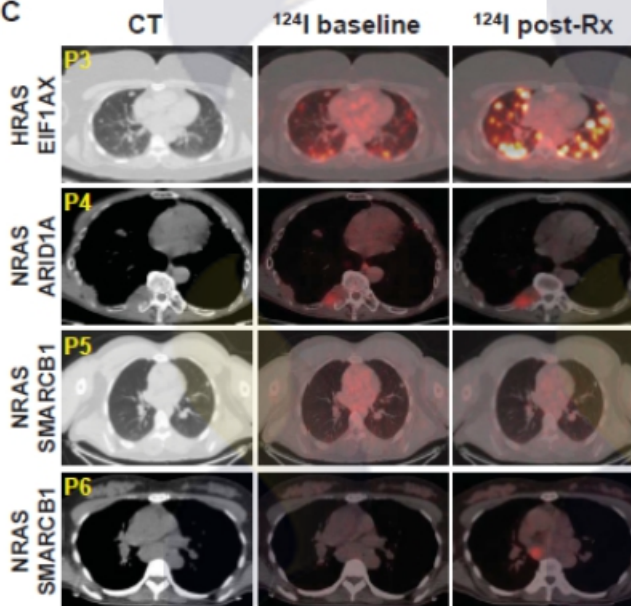
A



B



C



Gnana Krishnamoorthy

Mahesh Saqcena

Vera Tiedje

Brian Untch

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Aradhya Nigam

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John Blenis

Richard Koche

Jesper Maag

Support

RO1-CA50706 RO1-

CA249663 RO1-CA255291

Ludwig Center for Cancer

Immunotherapy

Jayne and Peter Flowers

Byrne Fund

Cohen fund

Cycle for Survival

MSK patients.

Clinical Trials

Alan Ho

Lara Dunn

Eric Sherman

David Pfister

Vatche Tchekmedyan

Mike Tuttle

Mona Sabra

Stephanie Fish

Laura Boucai

Steve Larson

Ravi Grewal

Keith Pentlow

Pat Zanzonico

Ronglai Shen

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Molecular Diagnostics Lab

SKI Institutional Cores

