Redifferentiation Therapies for Thyroid Cancer

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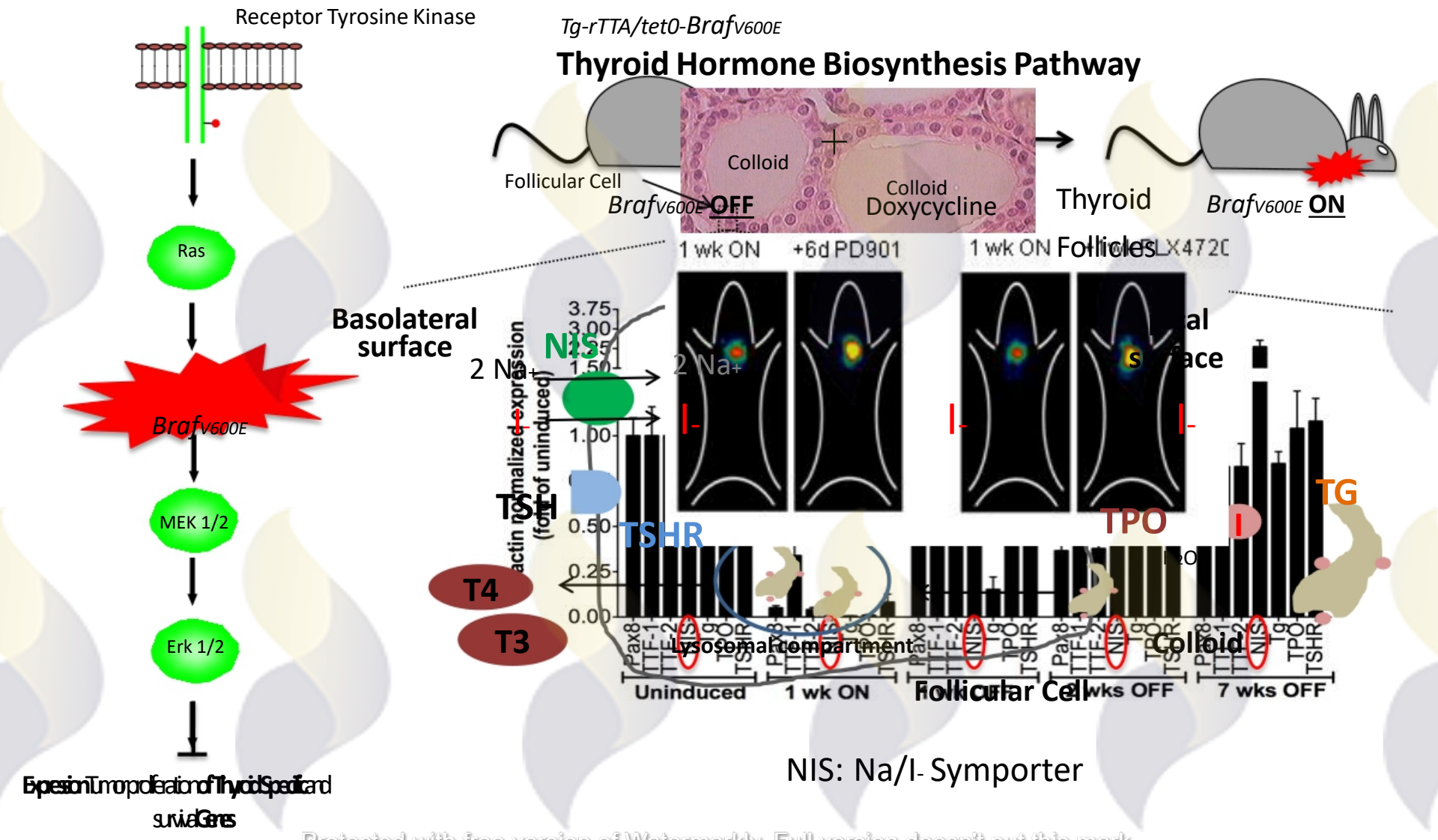
Mitogen-Activated Protein Kinase (MAPK) pathway activation suppresses expression of NIS in thyroid cancer



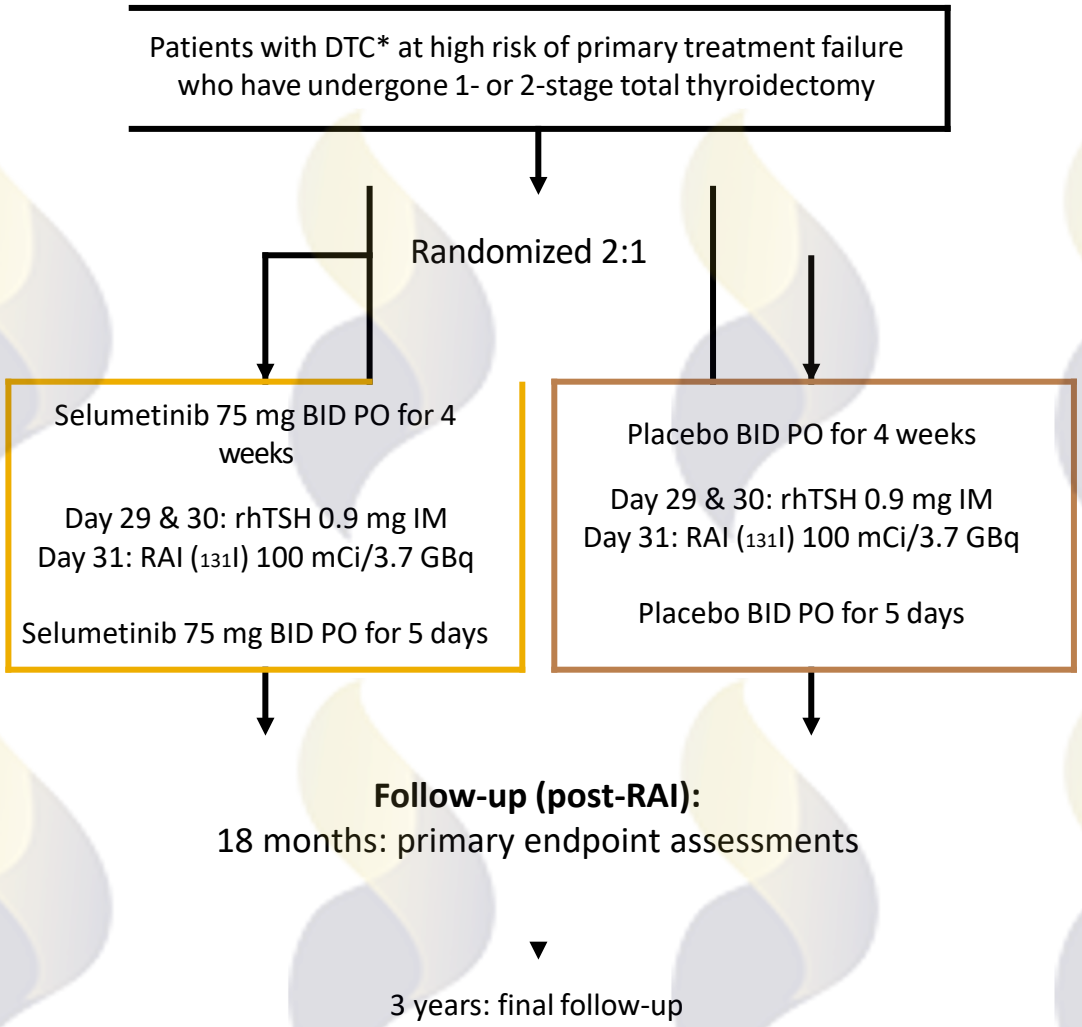
Chakravarty , D. et. al. J. Clin. Invest. 121(12):4700-4711, 2011.

Impact of selumetinib upon ^{124}Iincorporation

	N=20
Patients with new/increased ^{124}I incorporation after selumetinib	12/20
Patients who went on to receive therapeutic RAI	8/12

Ho, A.L. et. al., NEJM, 368:623-632, 2013

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)			

Population: full analysis set, data cut-off May 18, 2018

Ho A et al. J Clin Oncol 2022

Subgroup analyses of complete remission rate at 18 months

Group	Number (%) of patients with remission	Odds ratio	95% CI	2-sided p-value
***BRAF*-mutation positive**				
SEL + RAI (n=84)	30 (35.7)	0.96	0.45, 2.12	0.9242
PBO + RAI (n=41)	15 (36.6)			
***BRAF*-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)			

Population: patients with a confirmed *BRAF* and/or *NRAS* mutation; data cut-off May 18, 2018

Ho A et al. J Clin Oncol 2022

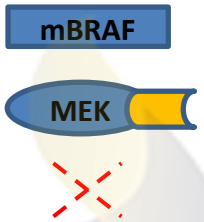
ASTRA Conclusions

- **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

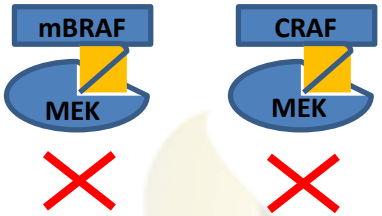
Ho A et al. J Clin Oncol 2022

Modest differences in MAPK pathway inhibition….

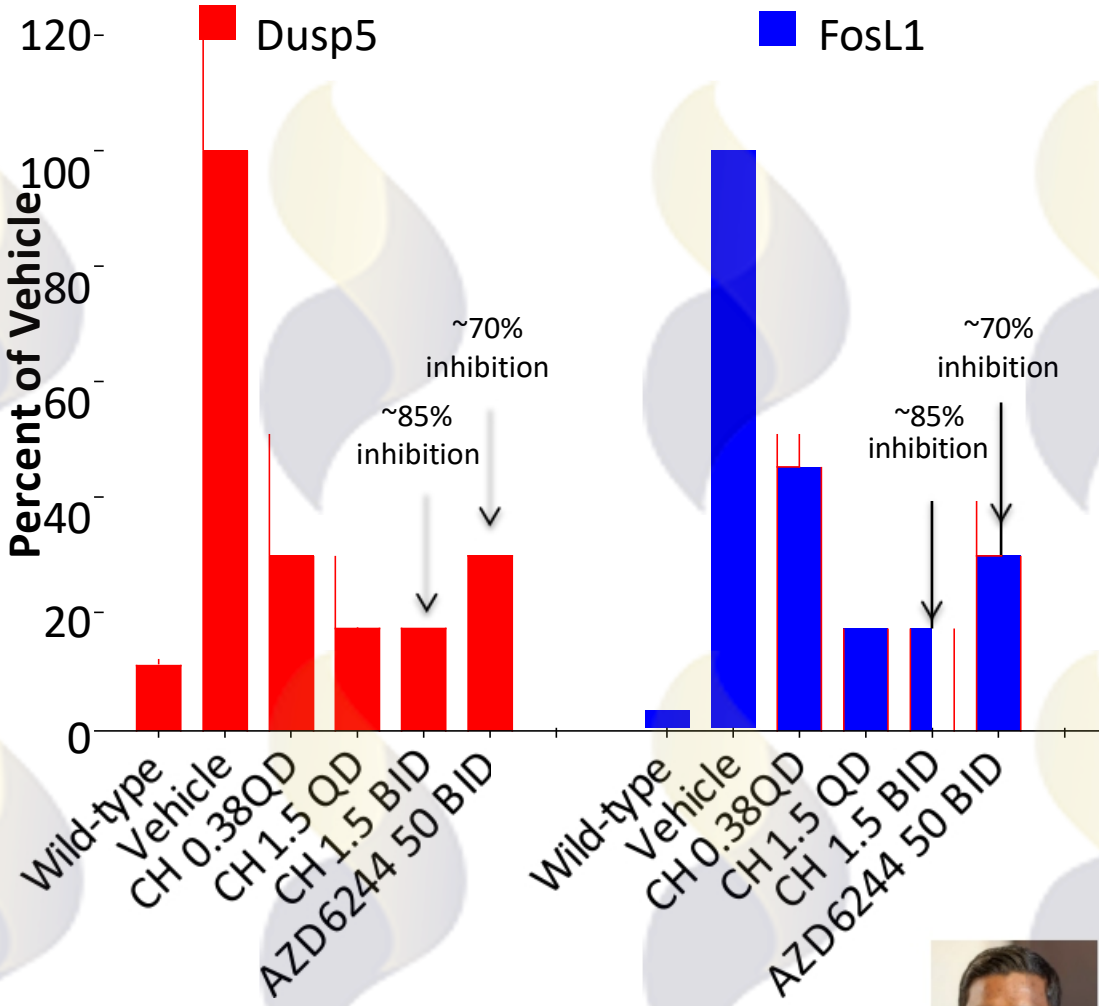
TPO-Cre LSL-BRAF^{V600E} PTC mouse model
(4.5 days of drug treatment)



AZD6244
(Selumetinib)

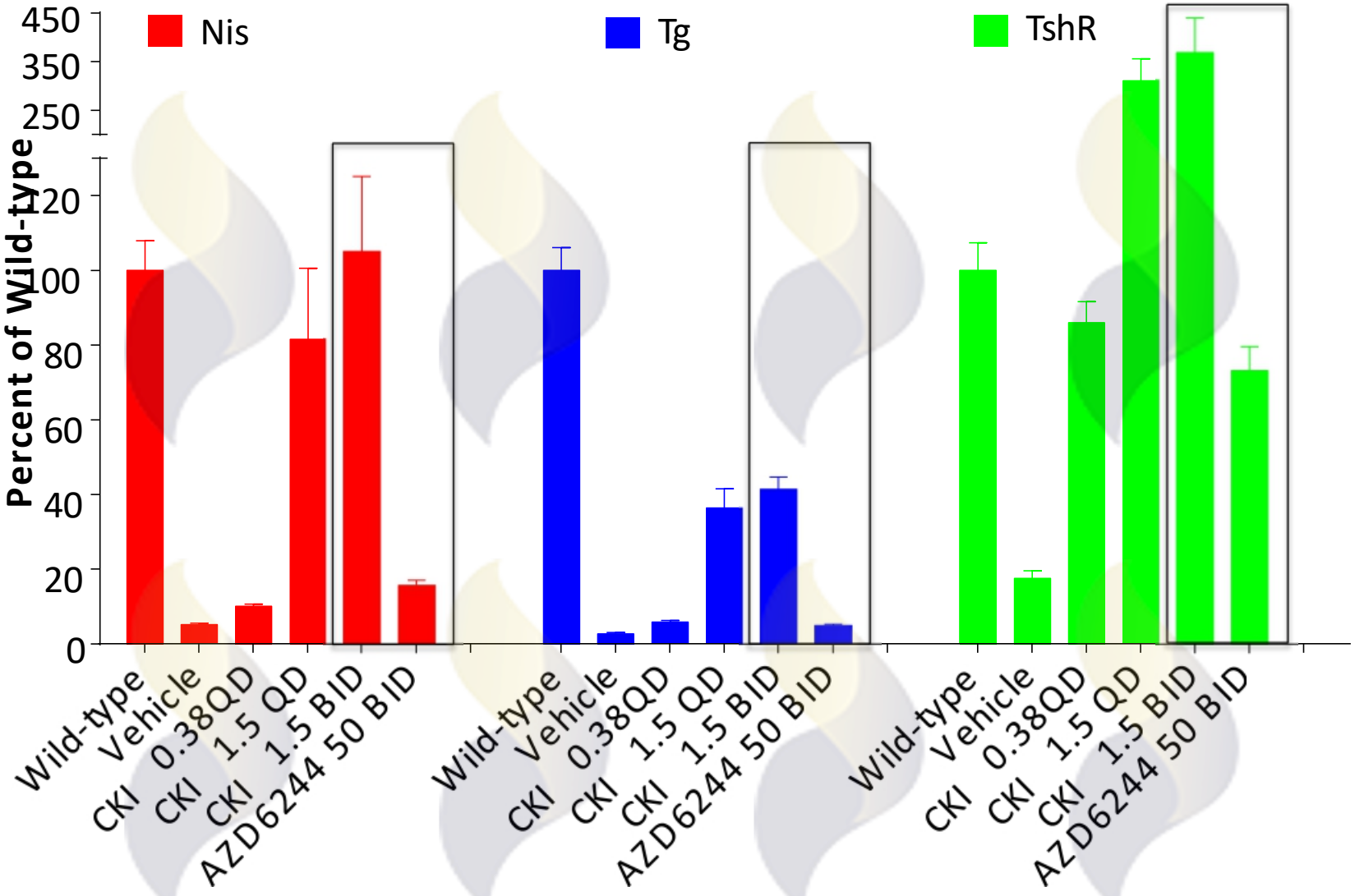


CH5126766
(CH or CKI)



Nagarajah, J. et. al., *JCI*, 2016

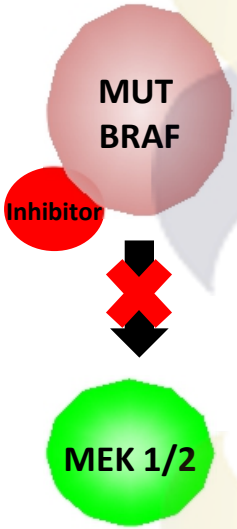
… translate to significant changes in iodine metabolism gene expression



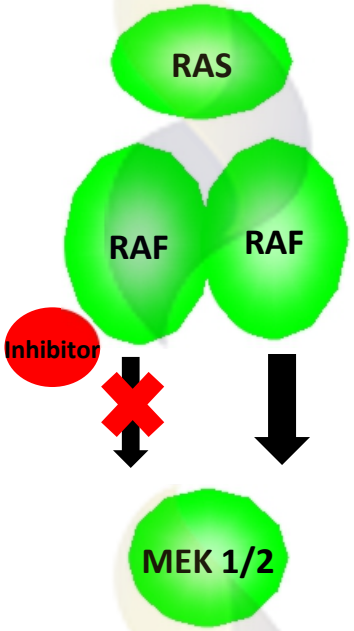
Nagarajah, J. et. al., *JCI*, 2016

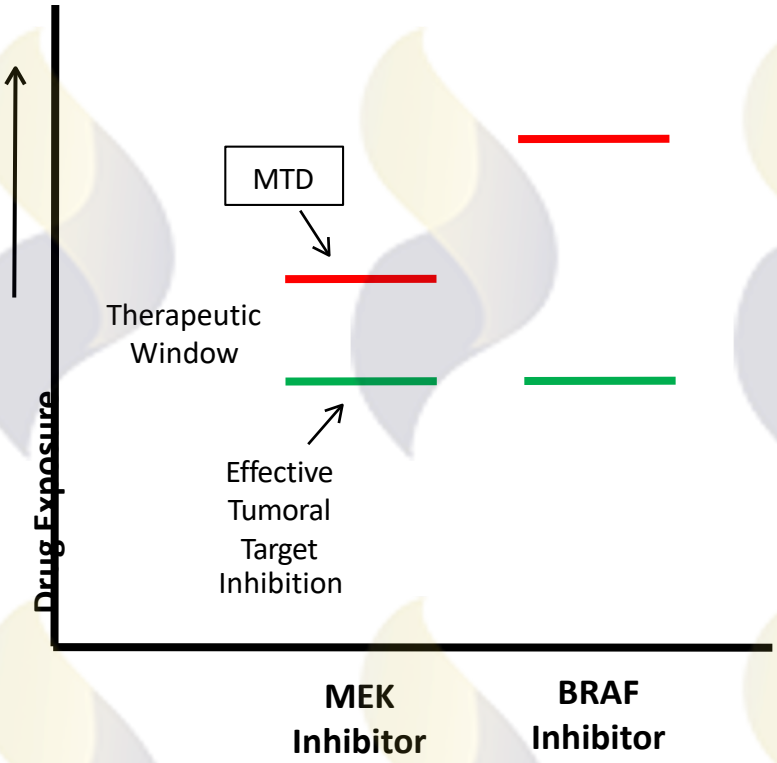
BRAF MUT Tumors: Alternatives to MEK Inhibition

BRAF Mutant Cell
(Tumor)



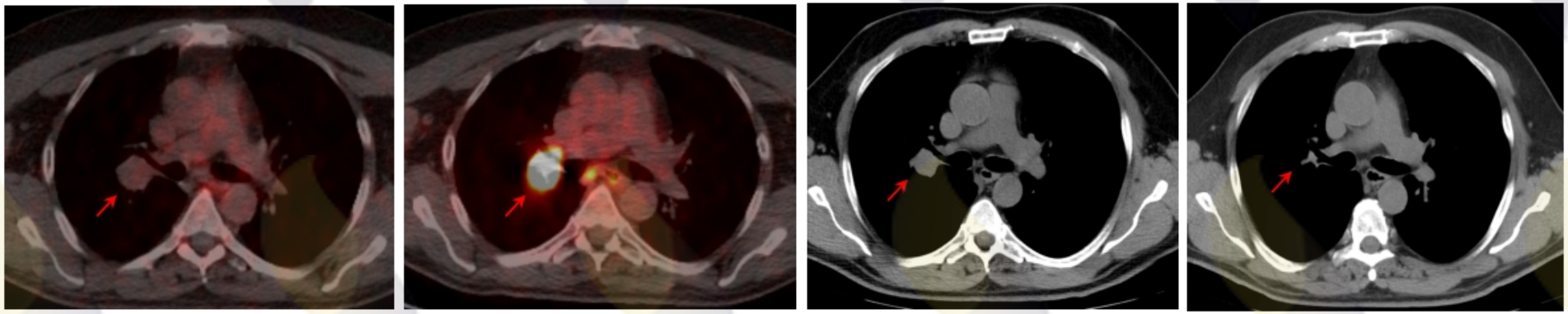
BRAF WT Cells
(Normal Tissues)



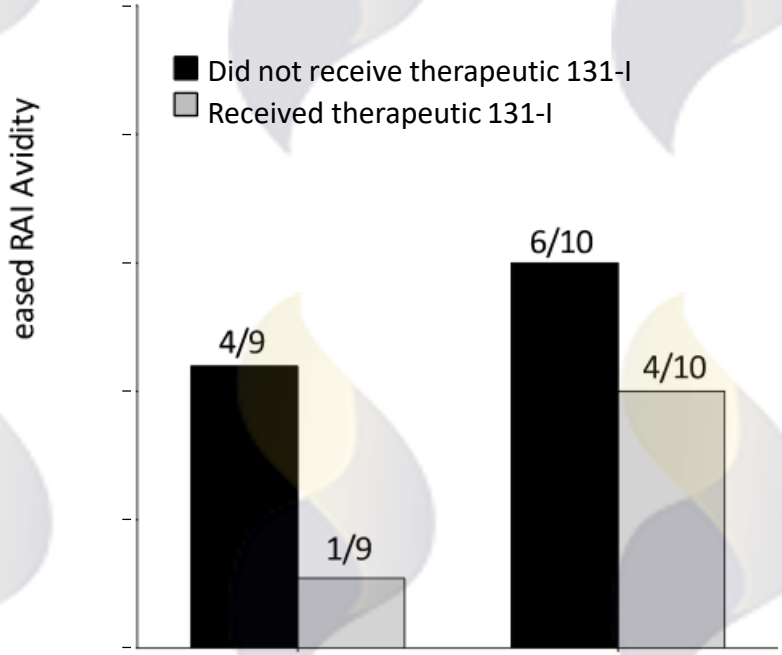


Poulikakos, Cancer Cell, 19: 11-15, 2011
Poulikakos et. al., Nature, 18:427-431, 2010

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



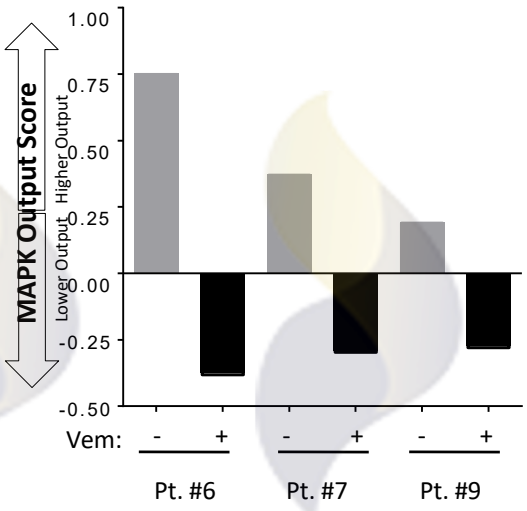
Baseline | Post-vemurafenib (~4 wks) | Baseline | 6 mos s/p vemurafenib + RAI

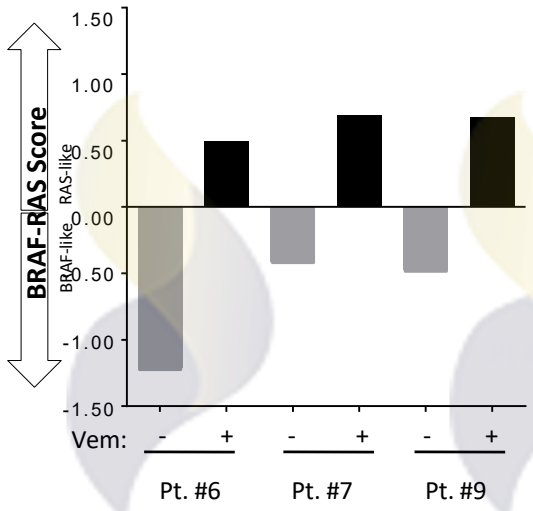


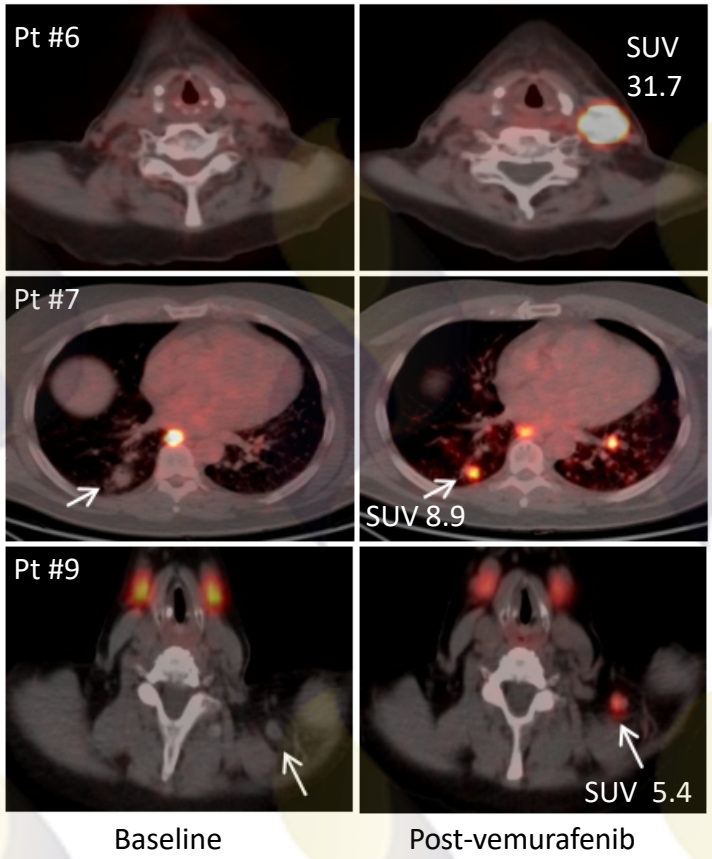
	RECIST Response Outcomes (PR+SD)
Selumetinib	1/9 (1 PR)
Vemurafenib	4/10 (2 PR, 2 SD)

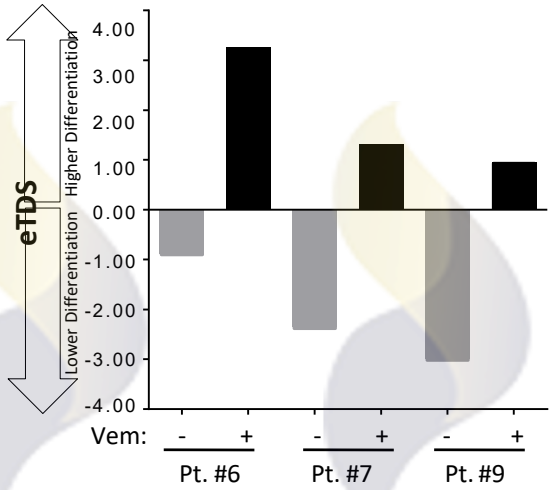
Dunn, L. et. al., *JCEM*, 2018

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



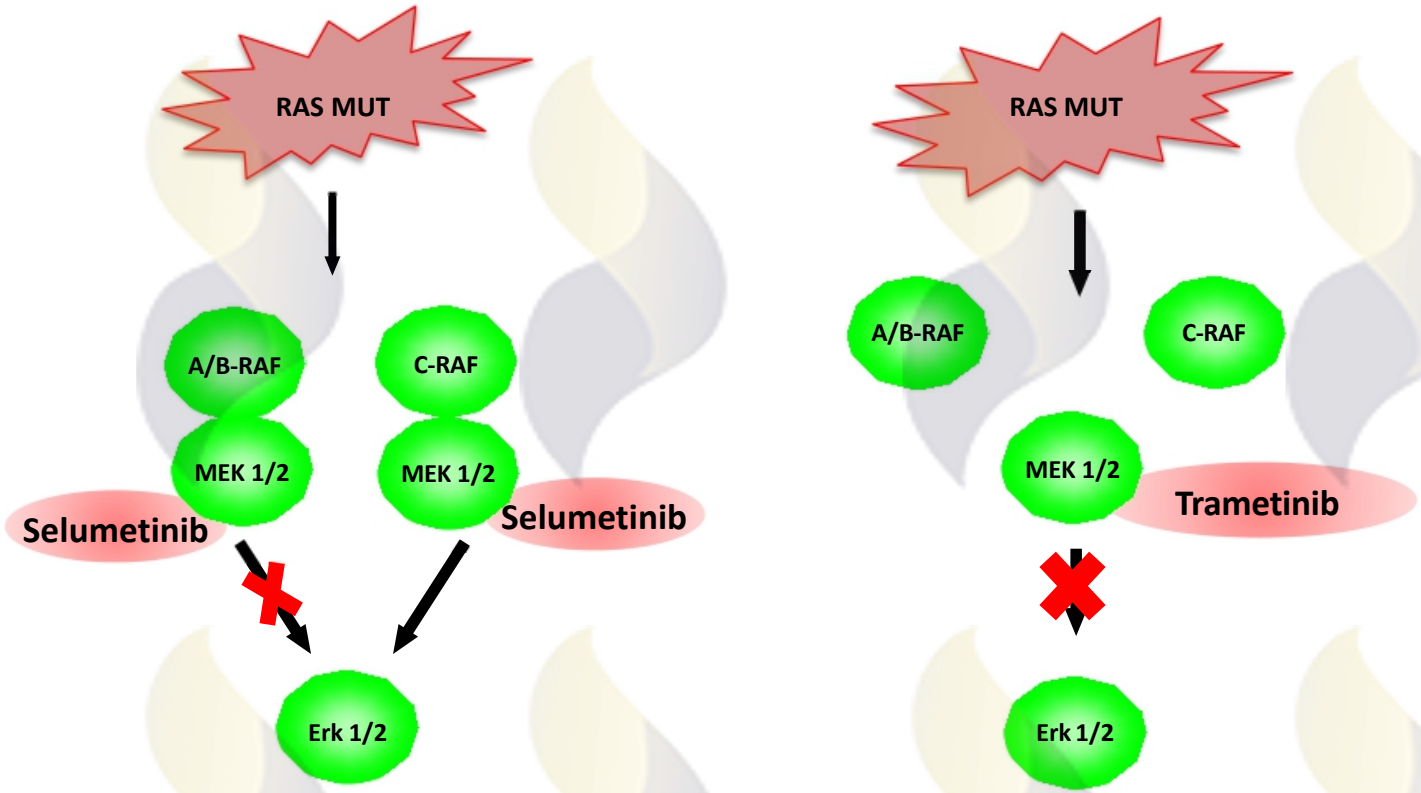






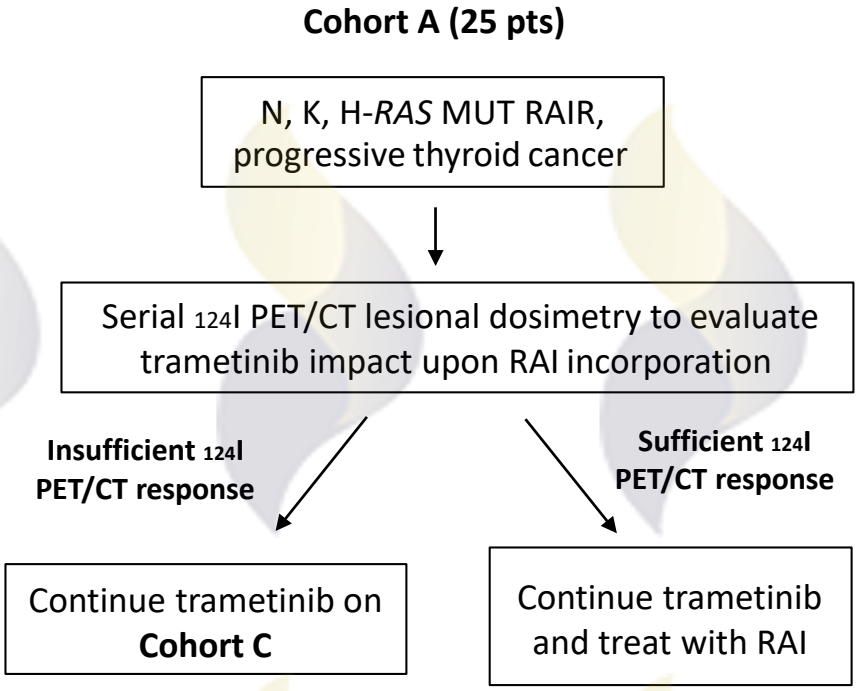
Dunn, L. et. al., *JCEM*, 2018

Not All MEK Inhibitors Are Created Equal



Lito, P. et. al., *Cancer Cell*, 25:691-710, 2014

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



<u>Primary Objectives (Cohort A)</u>: Evaluate PFS at 6 months and overall response at 6 months

NCI/CTEP; GlaxoSmith Kline; NIH R01

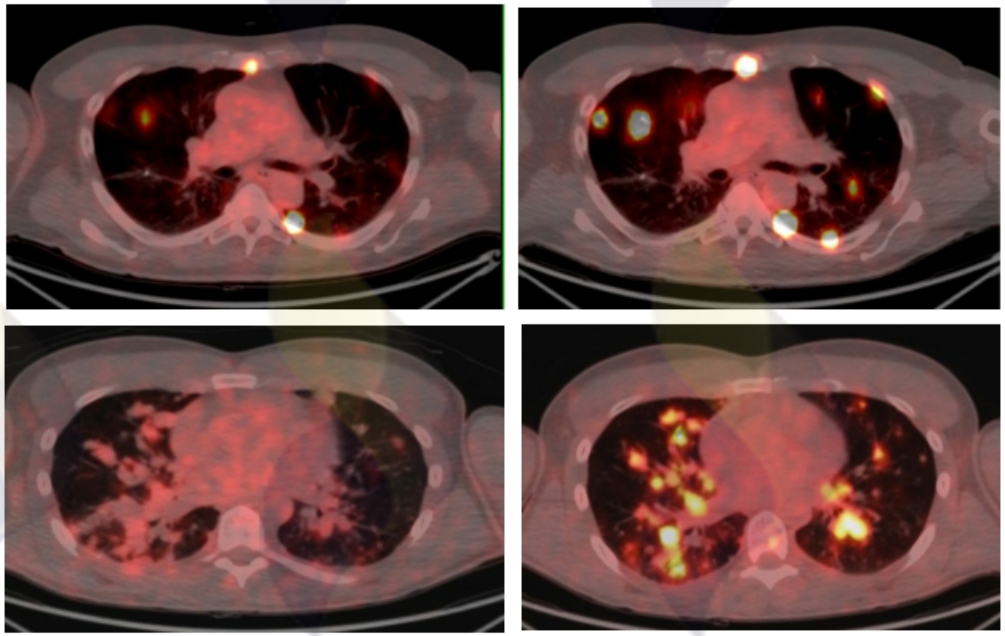
Cohort : *RAS* Mutant RAIR DTC

	n=25
Patients with new/increased ^{124}I 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)

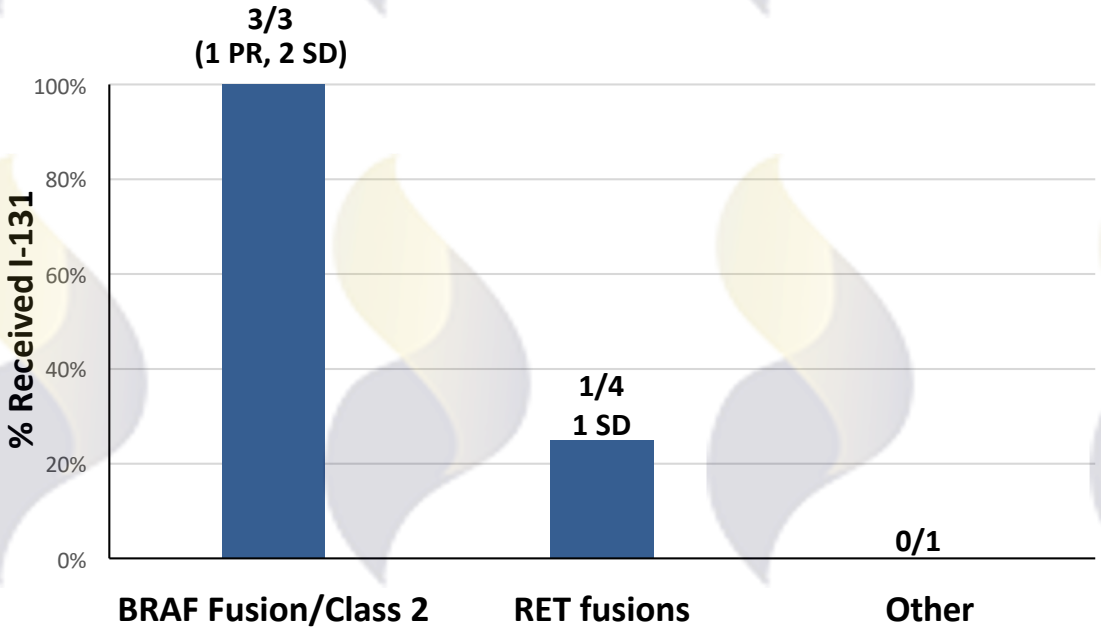
Patient A

Patient B

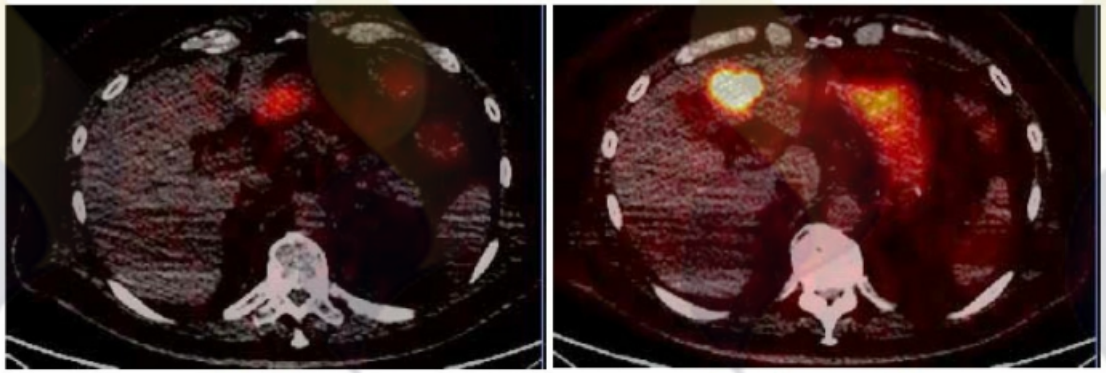


Baseline Post-Trametinib

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

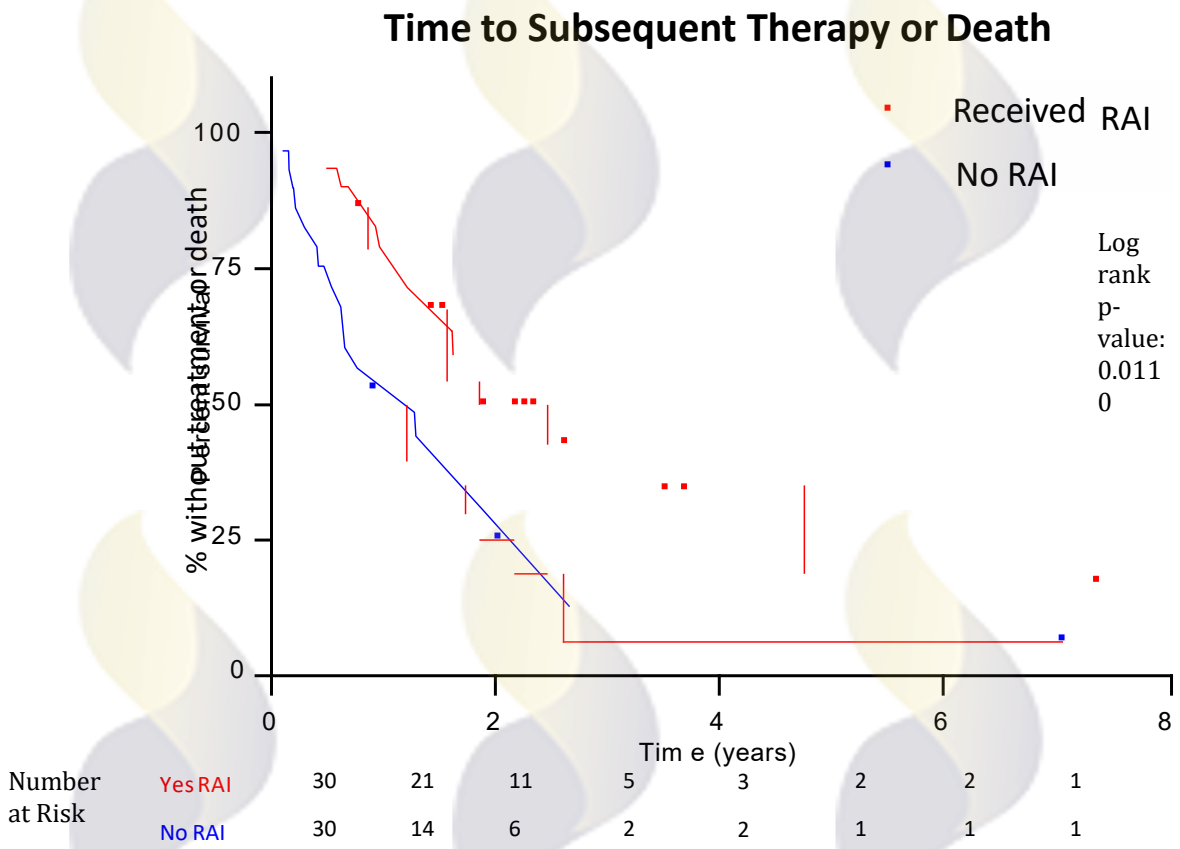


PRKAR2B-BRAF (PR; -69% regression)



Cumulative Redifferentiation Experience for RAIR Disease (n=69)

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



Efficacy of the phase 2 redifferentiation trials

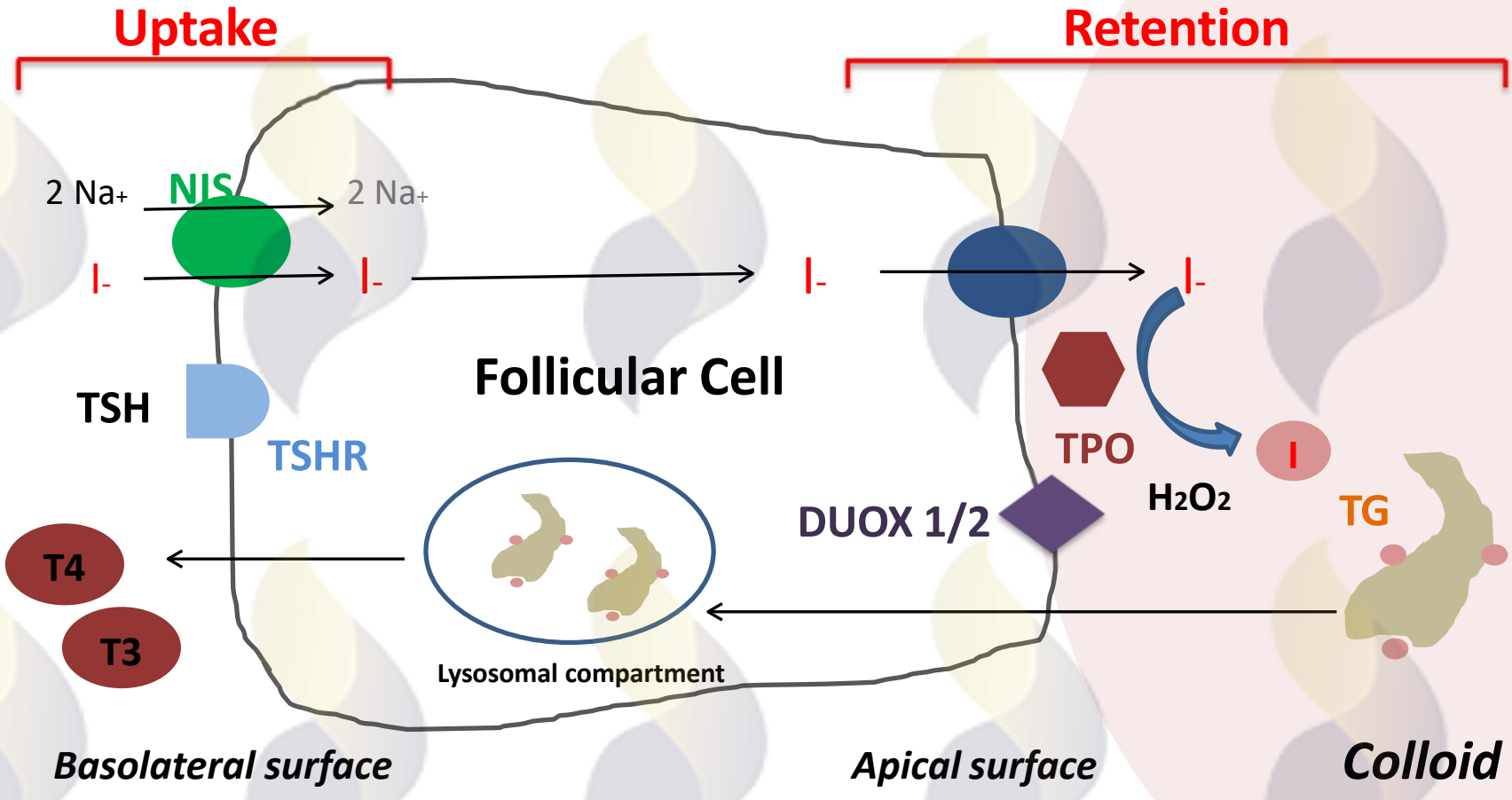
	Drug	n	Genotype	Increase of RAI uptake	Rx with RAI (n)	CR	PR	PFS
Ho, 2012	Selumetinib +/- ^{131}I	20	BRAF V600E RAS & other	12 (60%) ^{124}I PET/CT	8 (dosimetry, ≥ 20Gy)	0	25 % (5) (best PR)	-
Rothenberg 2015	Dabrafenib +/- ^{131}I	10	BRAF V600E	6 (60%) Dc ^{131}I WBS	6	0	20 (2) (best PR)	-
Dunn, 2018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

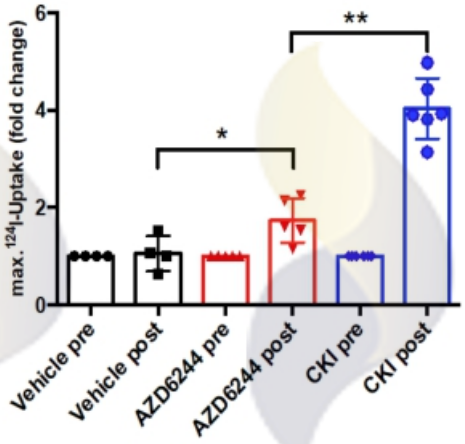
Thyroid Hormone Biosynthesis



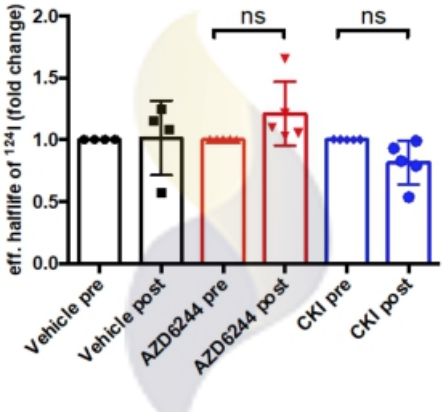
MAPK Inhibition in *BRAF* Mutant Mouse Models Do Not Impact Iodide Retention

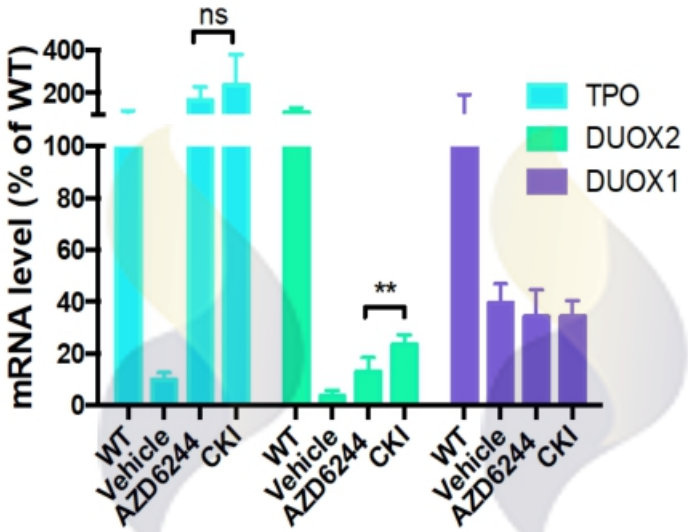
TPO-Cre LSL-BRAF^{V600E} PTC mouse model

Iodide Uptake



Iodide Retention





James Nagarajah Gnana Krishnamoorthy

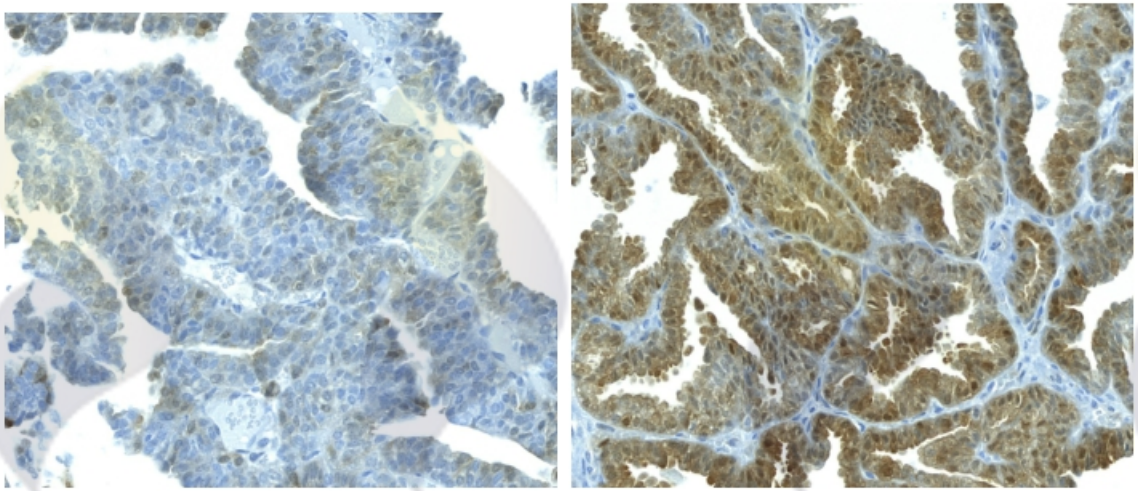
Combined BRAF-MEK Inhibition Increases Akt Phosphorylation

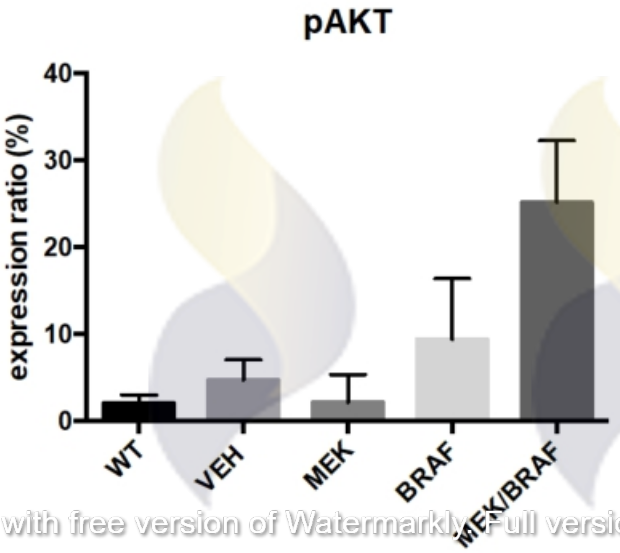
TPO-Cre LSL-BRAF^{V600E} PTC mouse model

Vehicle

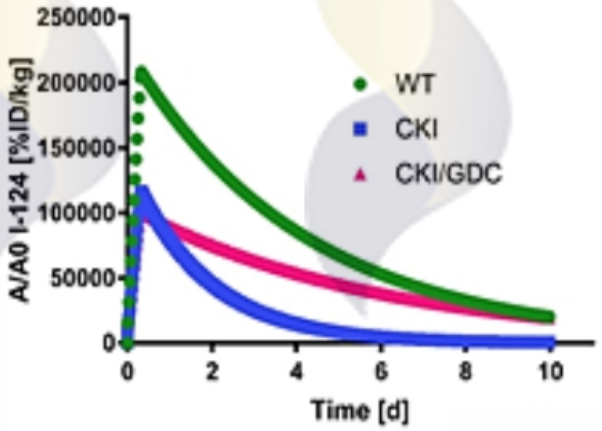
LGX818 + MEK162

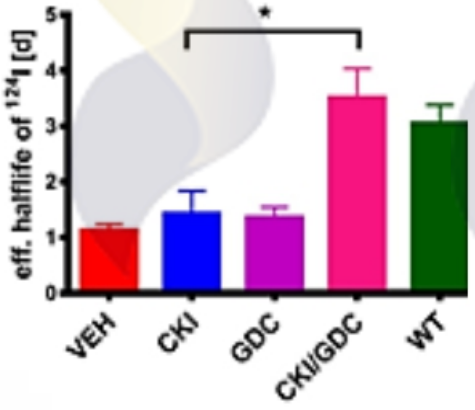
pS308-AKT





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





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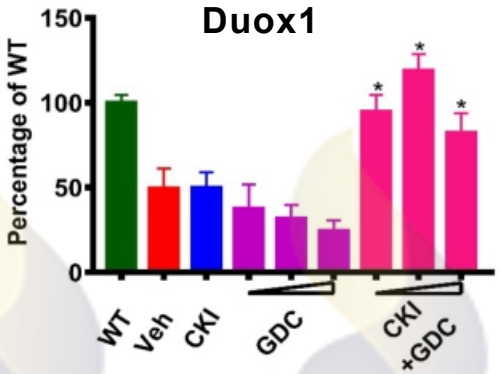
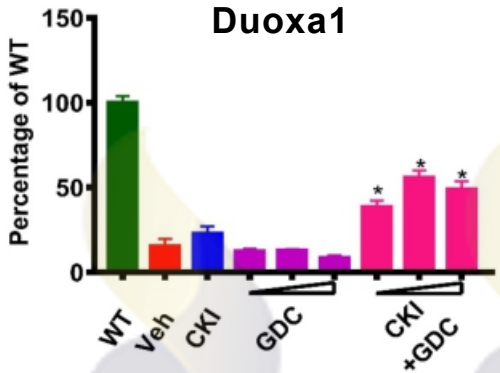
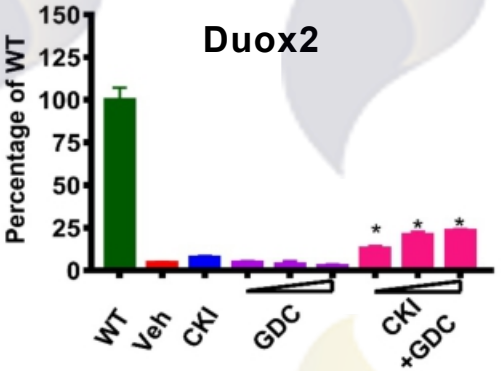
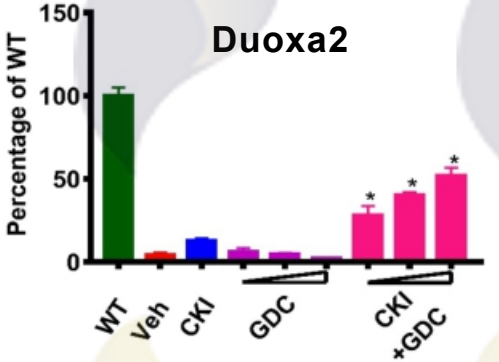
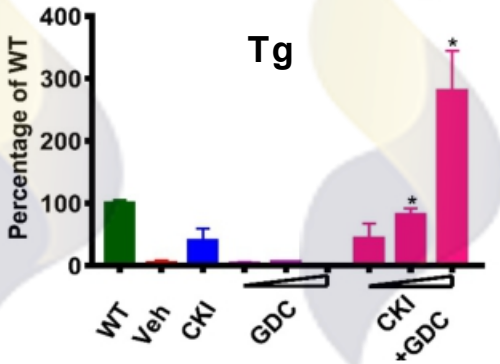
Duox1/2 Upregulation with Dual MAPK/PI3K Inhibition

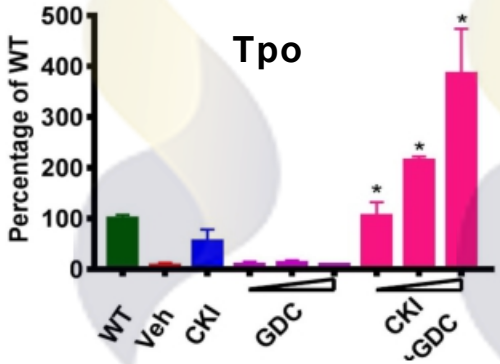


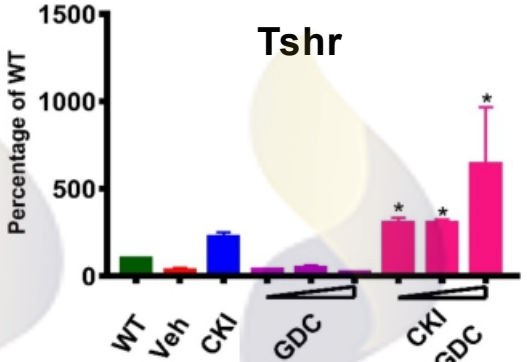












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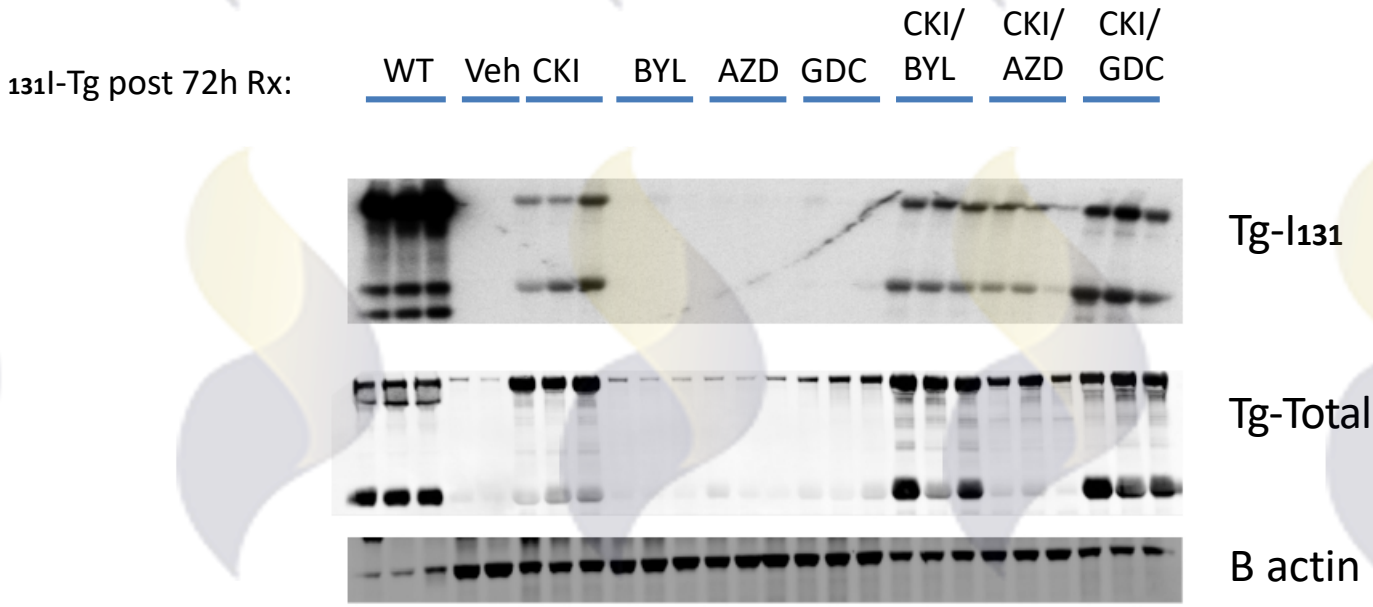
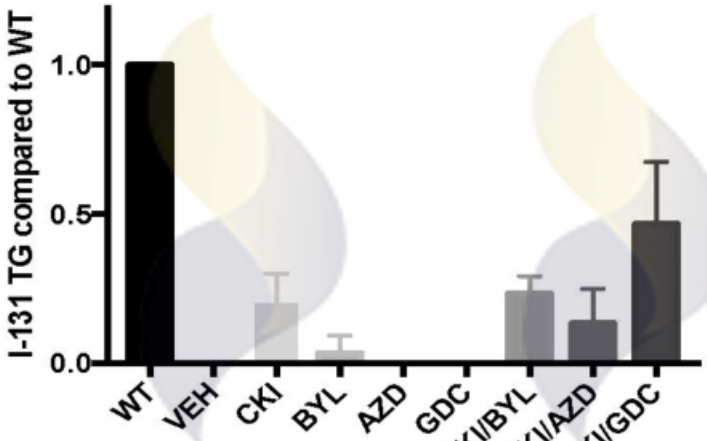
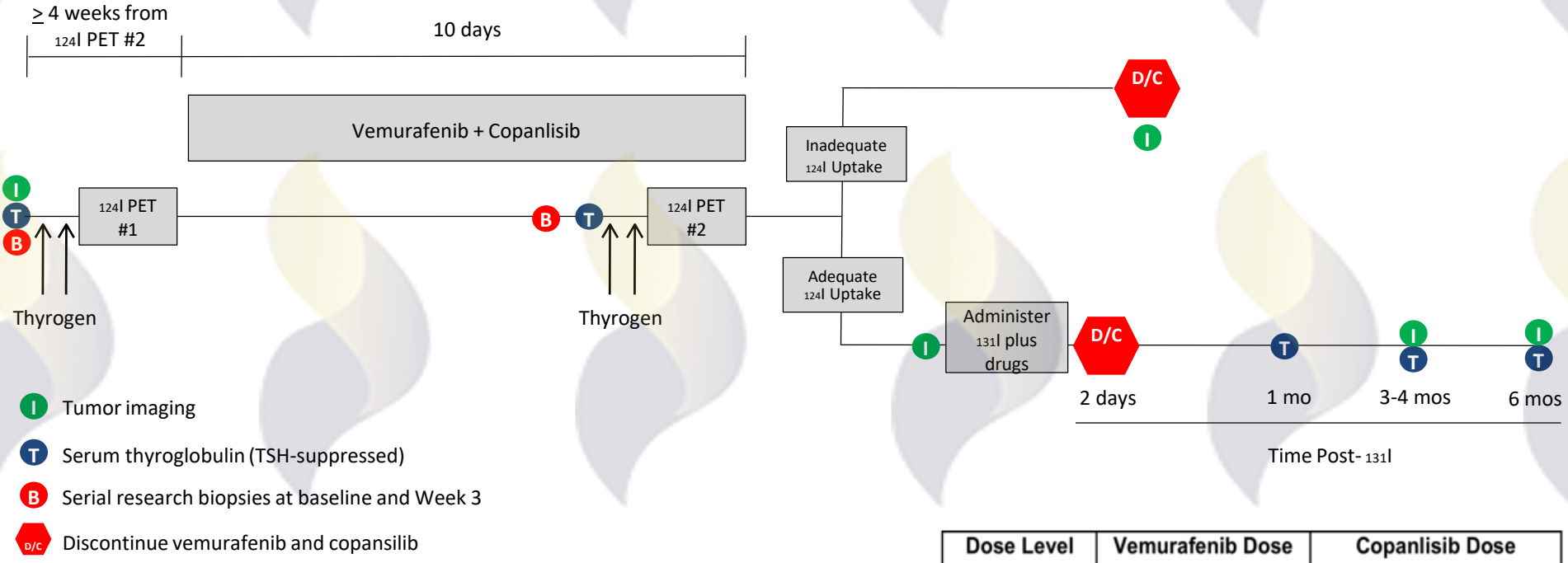
Effects of selective MAPK and/or PI3K pathway inhibitors on iodine incorporation into Tg





BYL: BYL719
AZD: AZD6482
GDC: GDC0941

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



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

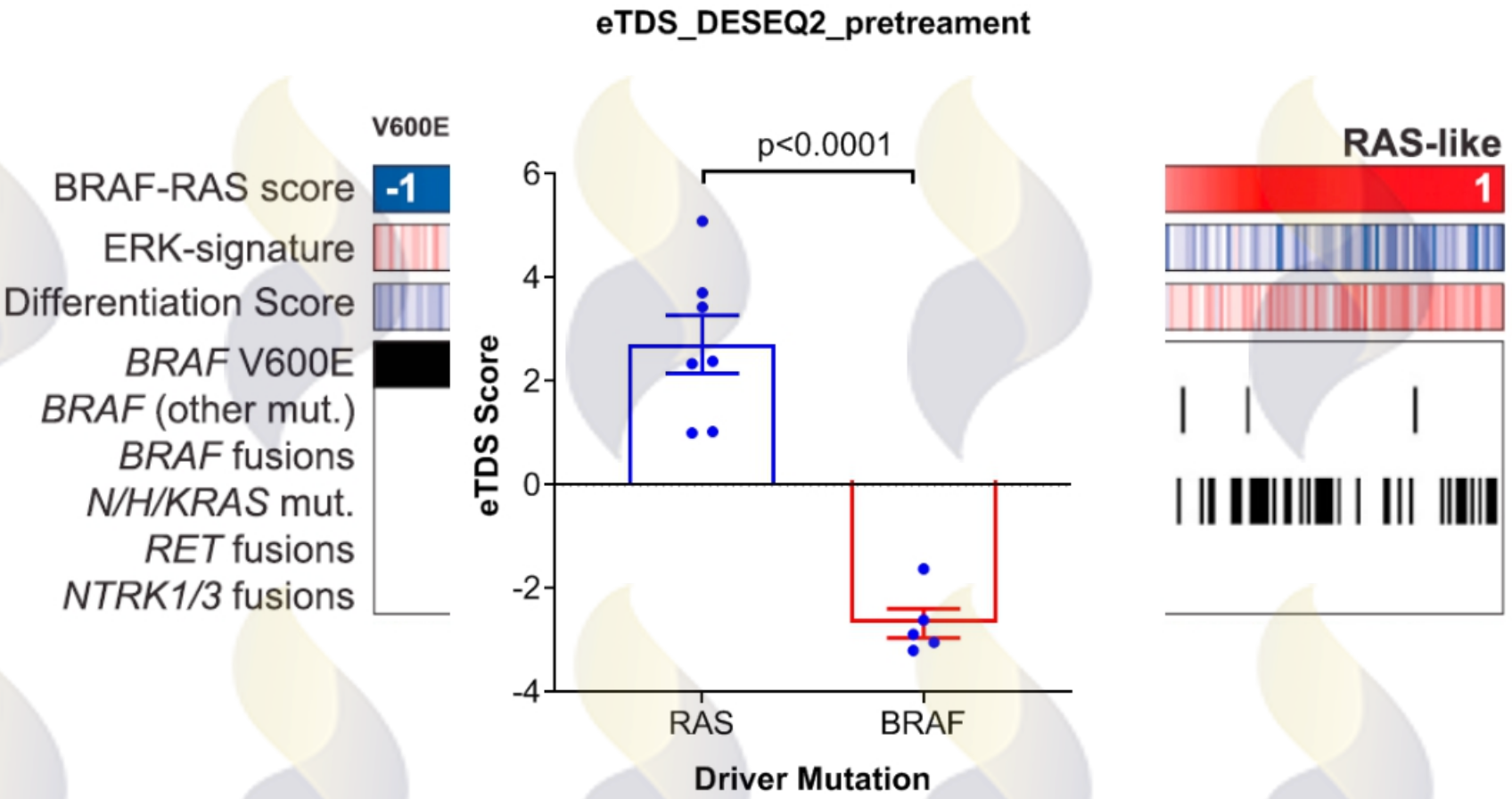
Primary Objective: To identify the maximum tolerated dose (MTD) of vemurafenib plus copanlisib for *BRAF* mutant, RAIR thyroid cancer patients.

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

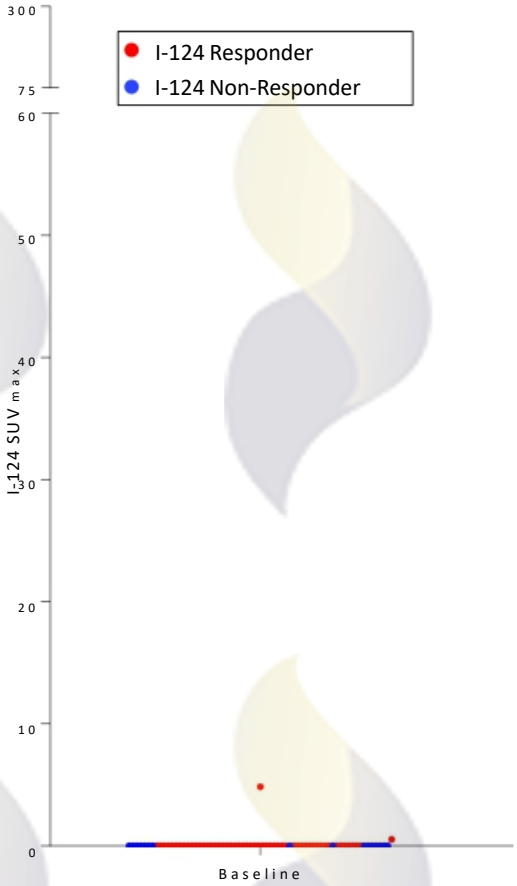
Bayer/Larson/Humm/Tuttle/Fagin

TCGA: Spectrum of thyroid-specific gene expression



Taken from TCGA, Cell 159:676-690, 2014

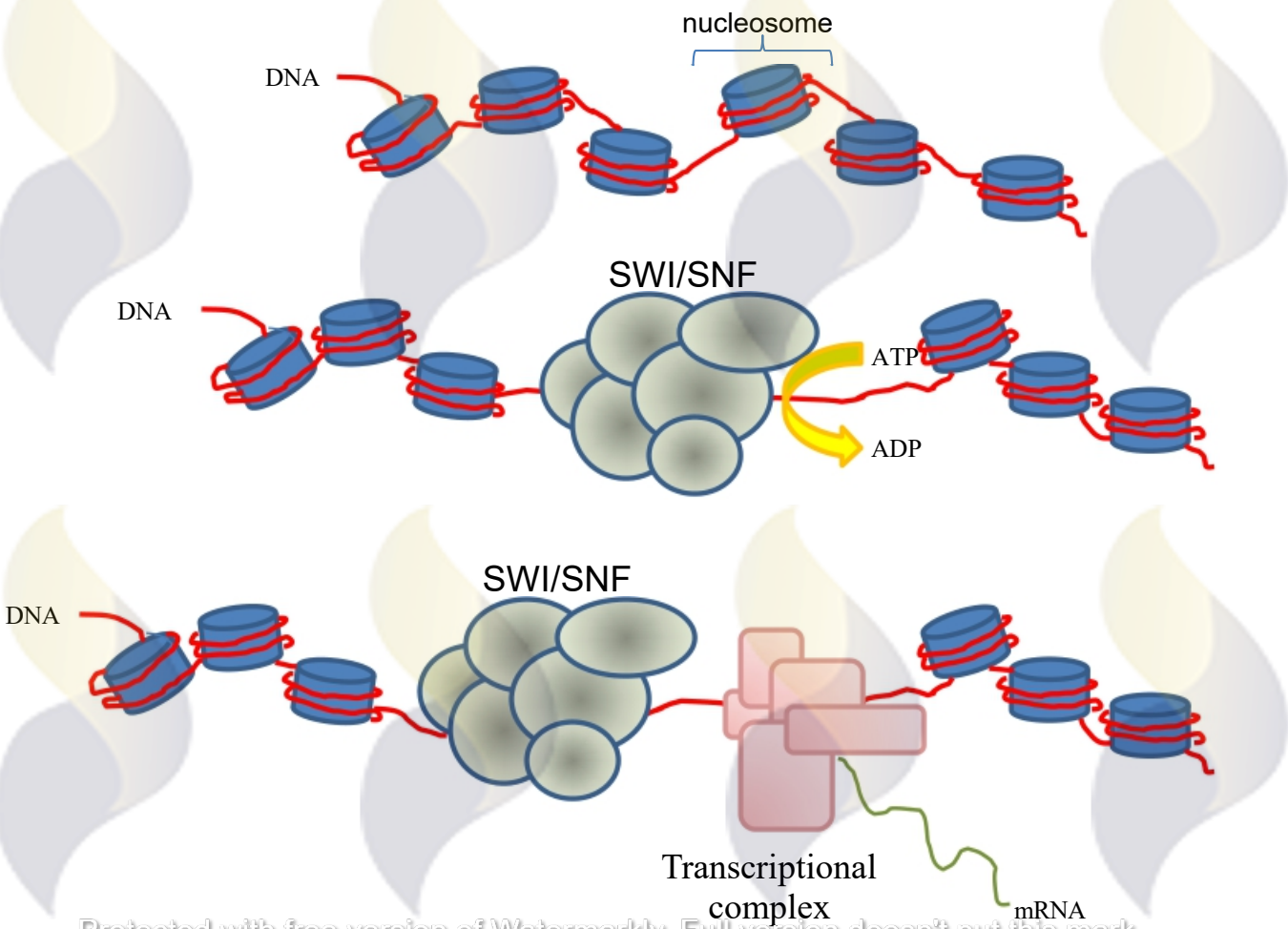
Baseline TG as Marker of Differentiation: Vemurafenib Redifferentiation



Dunn, L. et. al., *JCEM*, 2018

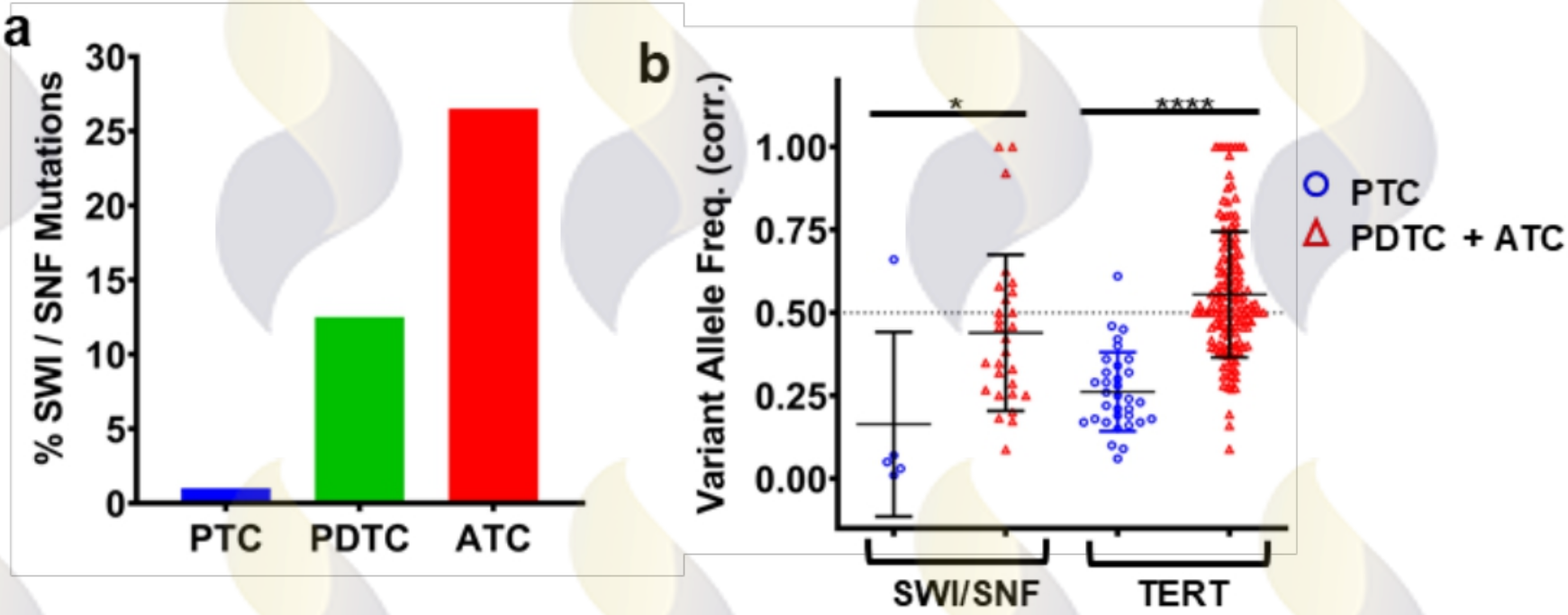
SWI/SNF Complexes

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

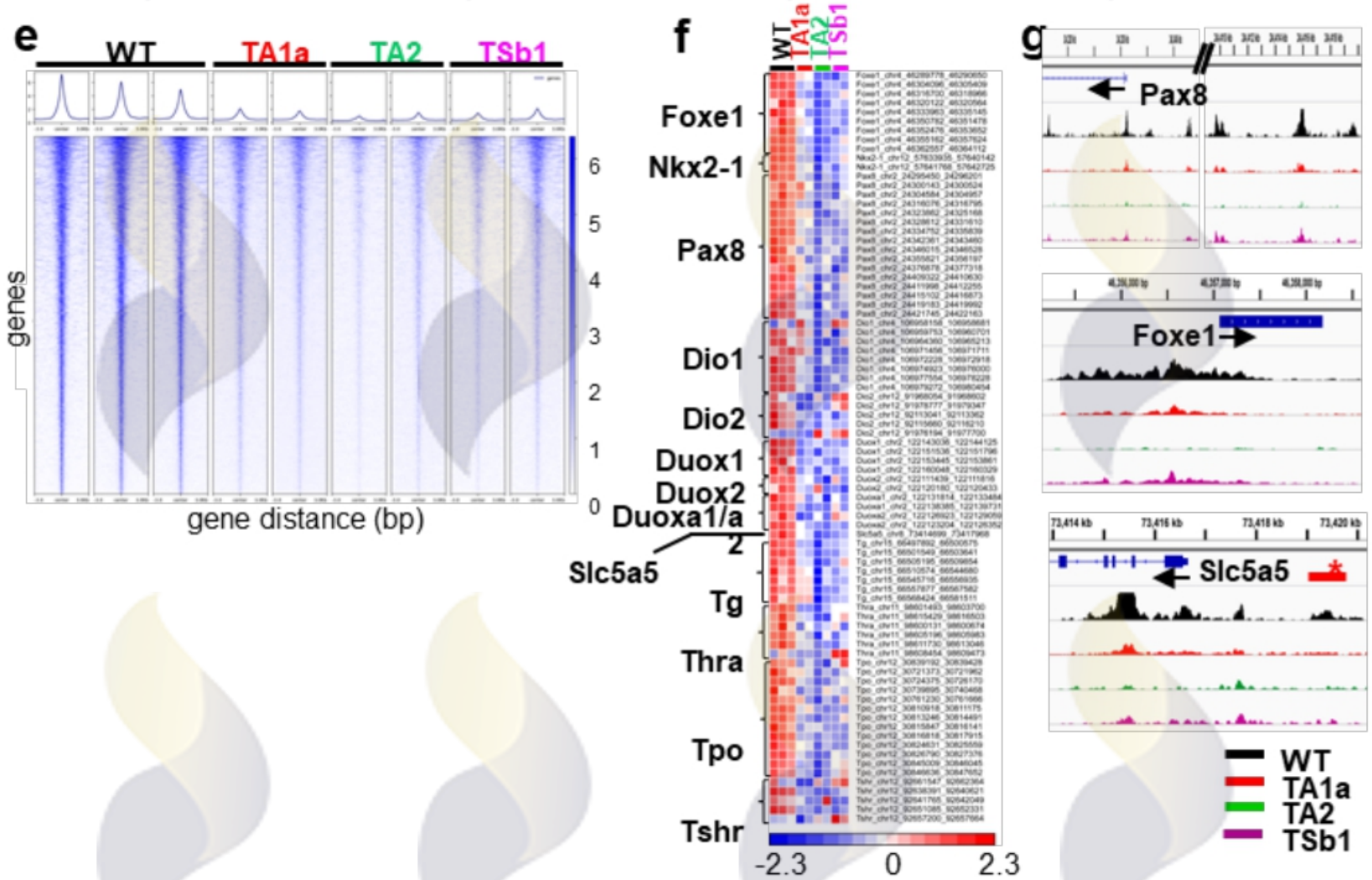


SWI/SNF mutations in thyroid cancer

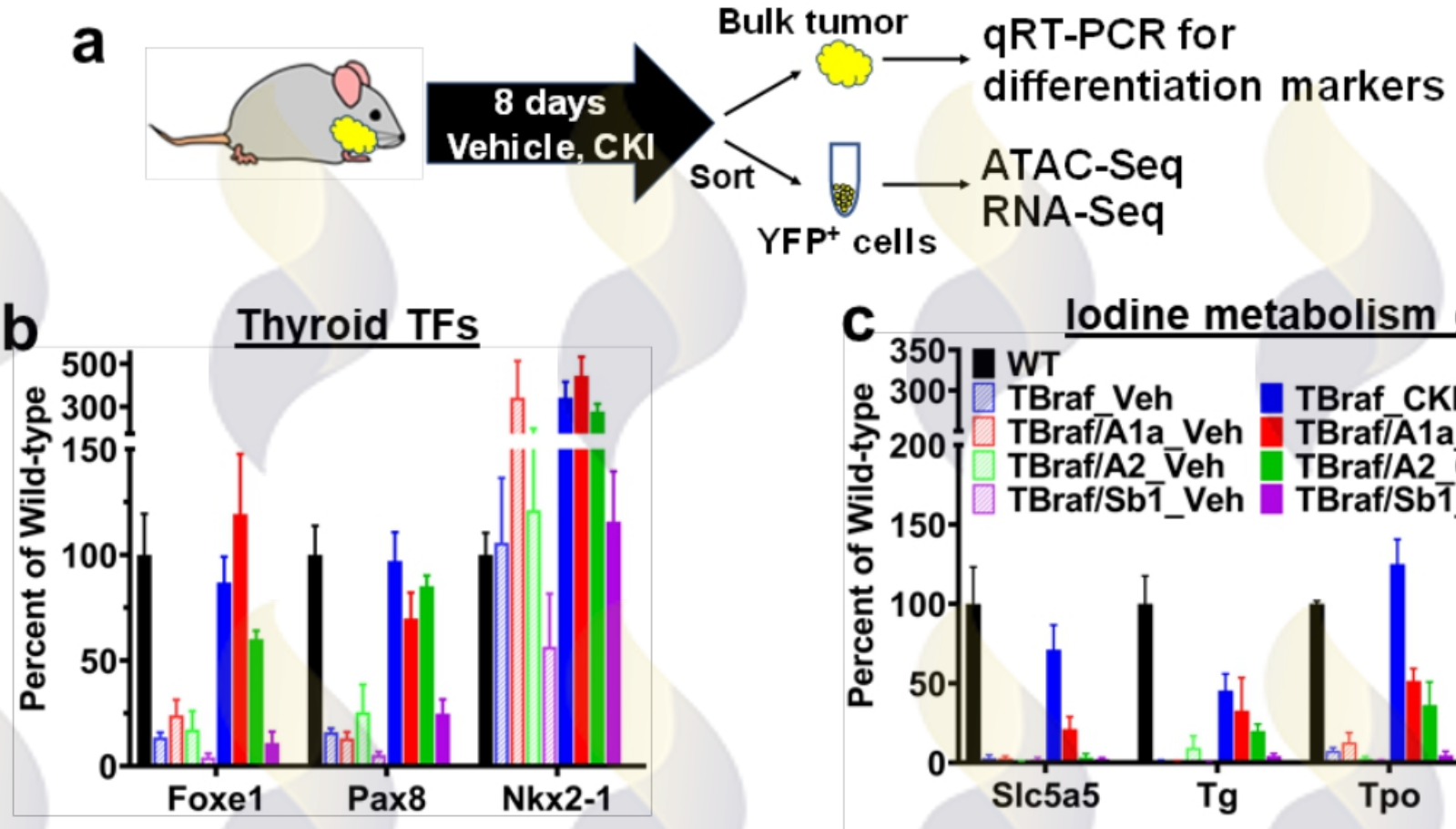
Multisubunit complexes that mobilize nucleosomes and remodel chromatin.



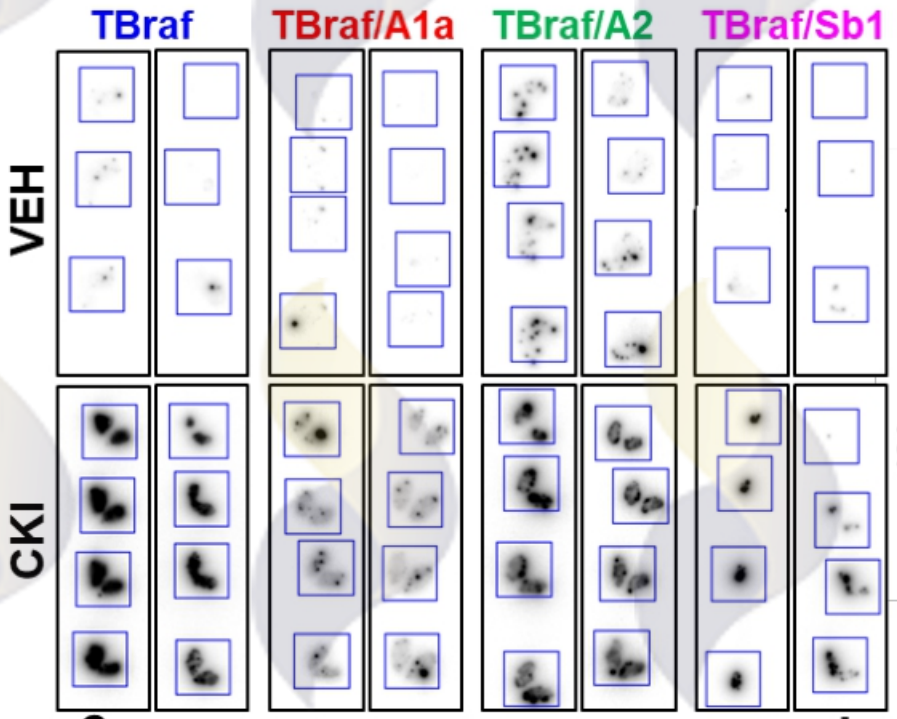
Landa I. J Clin Invest 2016.

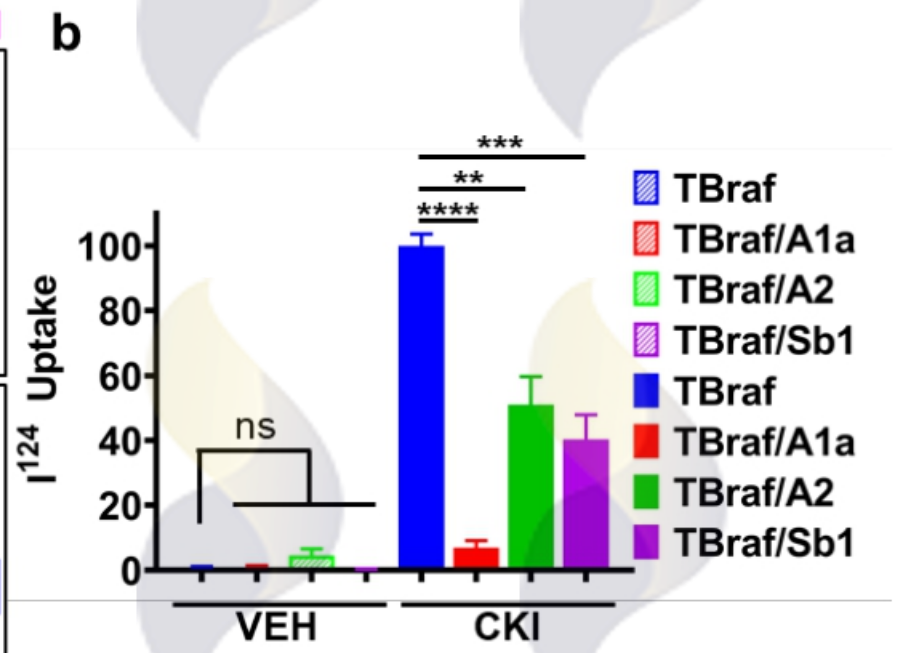


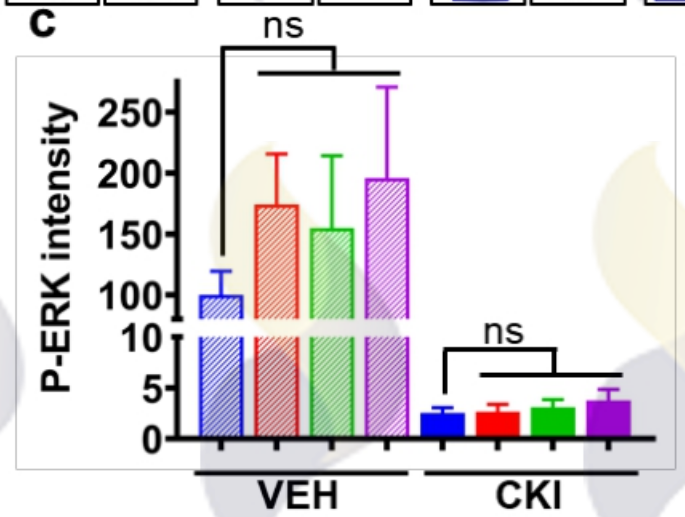
Saqcena M. Cancer Discovery. 2021

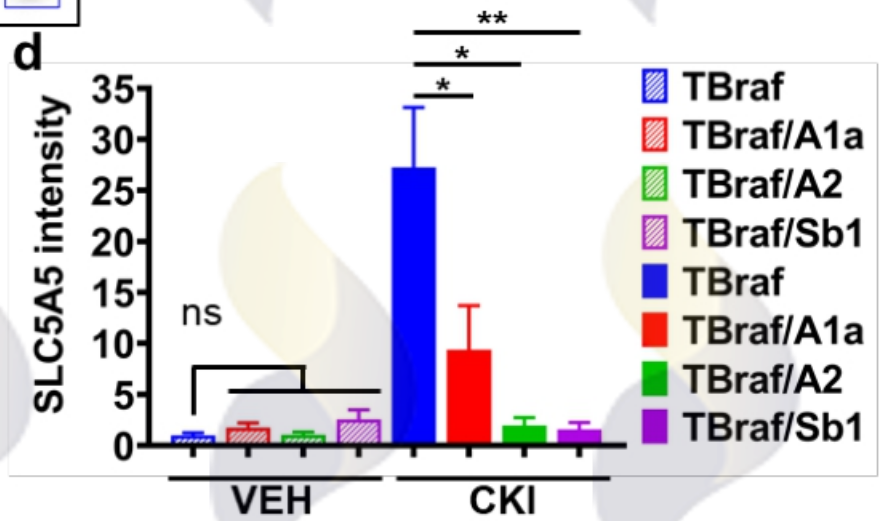


Saqcena M. Cancer Discovery. 2021









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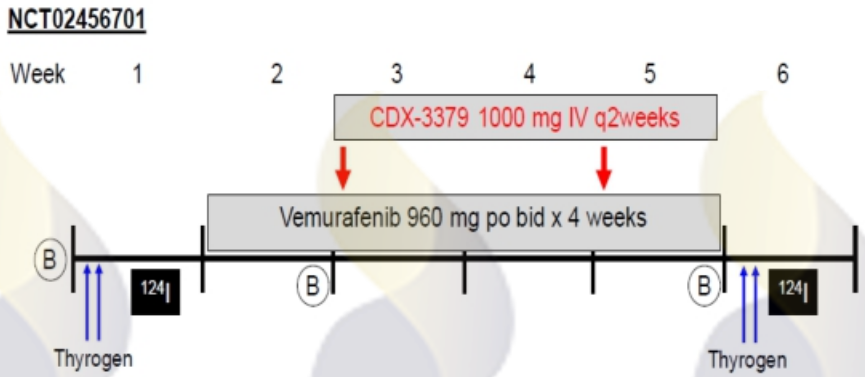
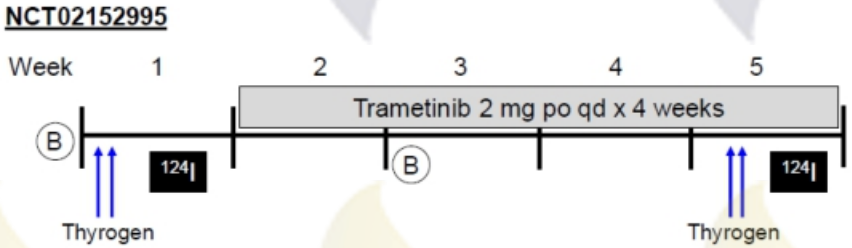




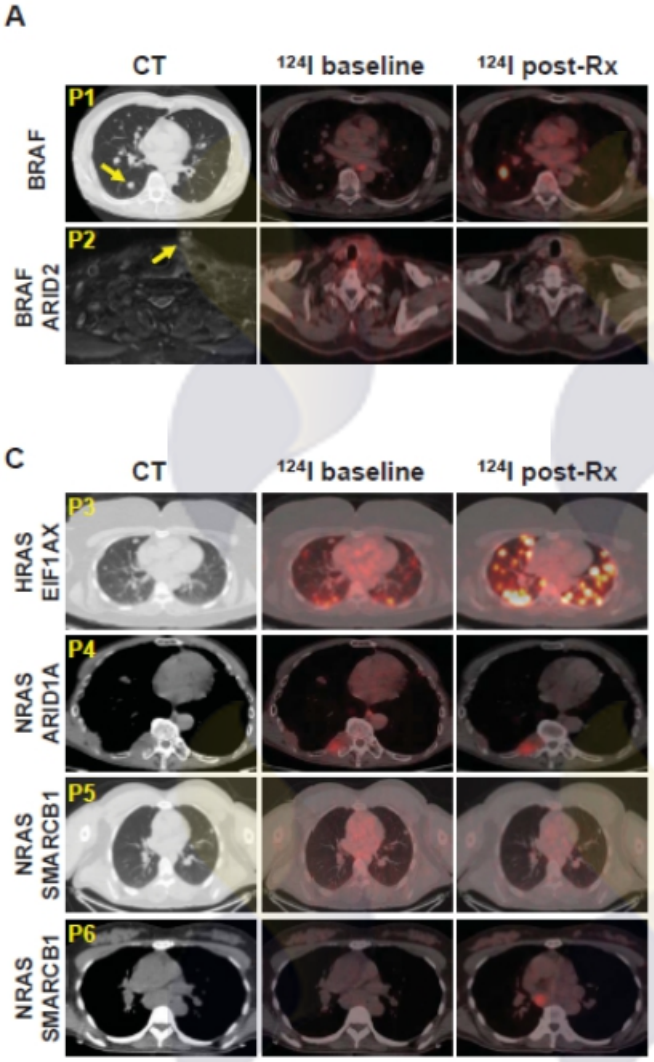
25 patients

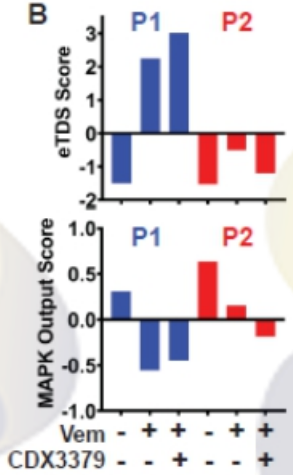
Responders

0/15 with A1a, A2 or Sb1 alterations

Non-responders

3/10 with A1a, A2, or Sb1 alterations





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Ludwig Center for Cancer Immunotherapy
Jayme and Peter Flowers
Byrne Fund
Cohen fund
Cycle for Survival
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