2025 City of Hope Multidisciplinary Thyroid Cancer Symposium

Mechanisms of Thyroid Tumor Resistance to Targeted Therapies

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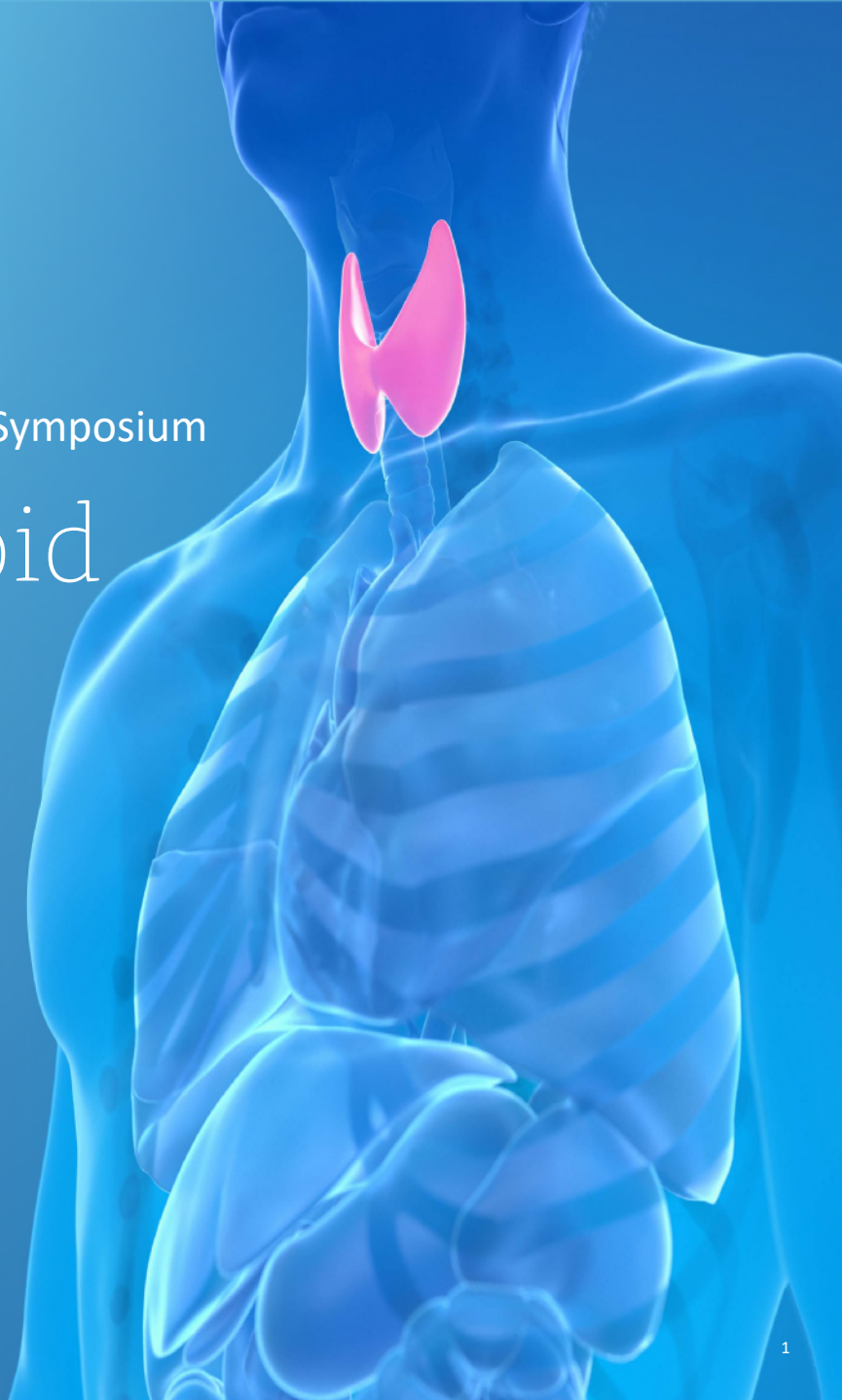


Disclaimer

This is a Non-CME Accredited Presentation.

I have not conflicts of interest on this Presentation

Disclosure:
Advisory Board Member, Affyimmune

Learning Objectives

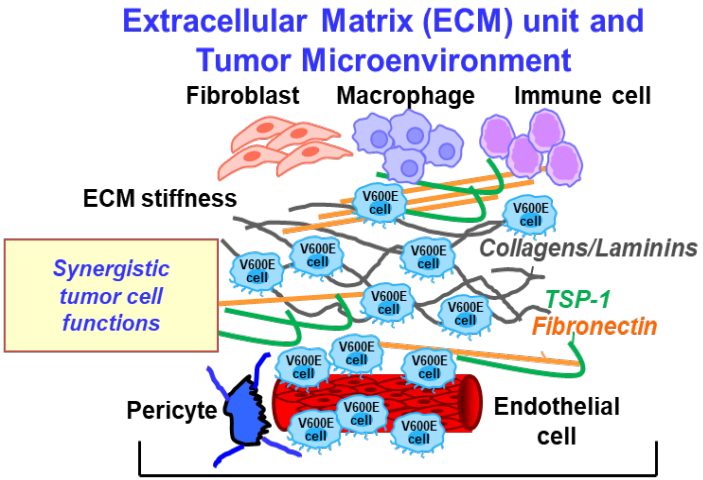
Targeted therapies (precision oncology)

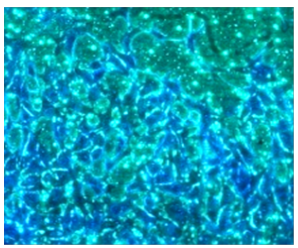
Clonal evolution in thyroid carcinoma (Cell autonomous)

Microenvironment (Non-cell autonomous)

1. Translational models of cell autonomous resistance in invasive thyroid cancer

2. Role of stem cell-like pericytes in resistance to BRAF^{V600E} inhibitors and tyrosine kinase inhibitors (TKI)



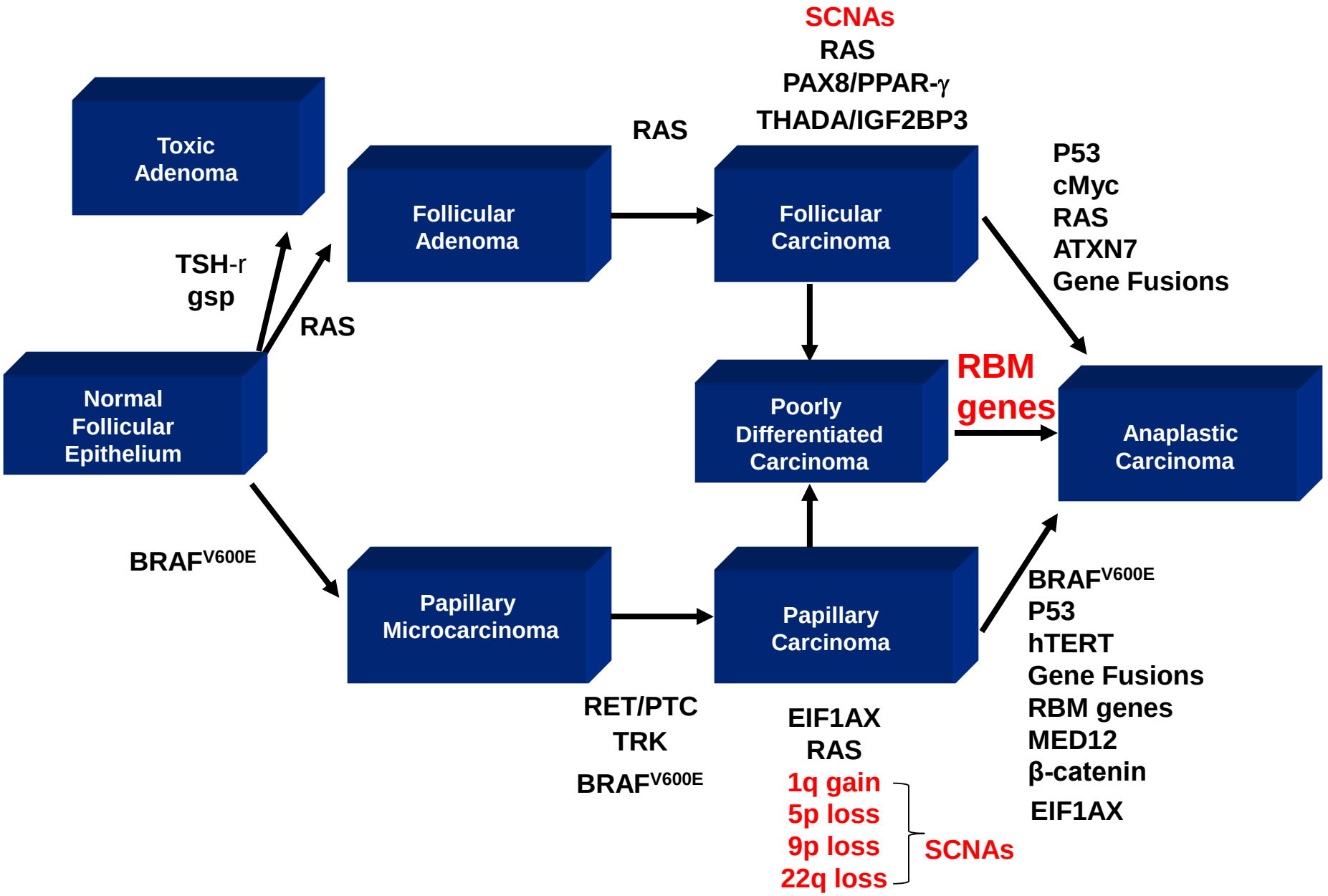


Migration and invasion of BRAF^{V600E} positive PTC cells towards target organs through metastasis

ThyCa progression

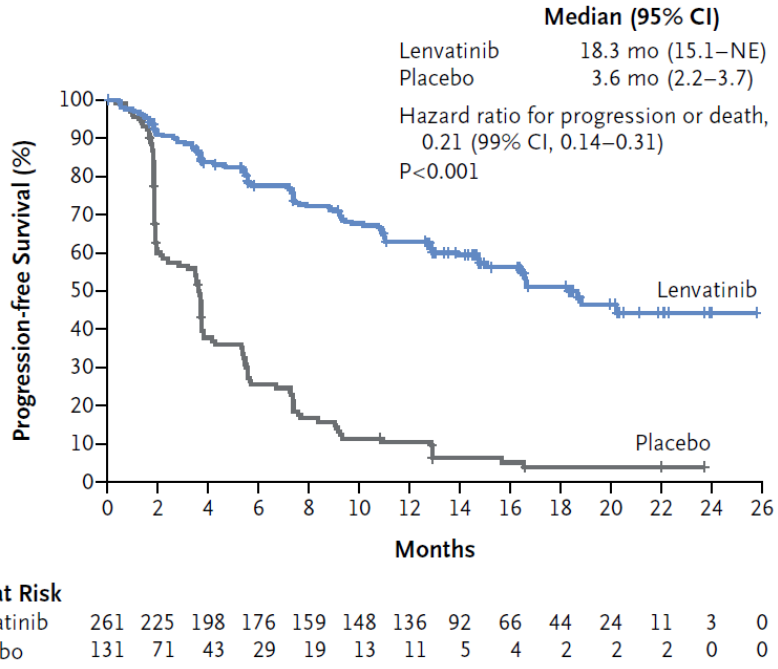
Duquette M, et al...and Nucera C.

Thyroid Carcinoma Coding (Onco)Genes



Tyrosine kinase inhibitors (TKIs) in Clinical Trials for Thyroid Cancer

The median progression-free survival was 18.3 months with Lenvatinib as compared with 3.6 months with placebo (P<0.001)



Schlumberger M, et al and Sherman SI, NEJM 2015

Outcome	Lenvatinib (N=261)	Placebo (N=131)
Progression-free survival		
Primary analysis, IRR and ITT populations‡		
Median (95% CI) — mo	18.3 (15.1–NE)	3.6 (2.2–3.7)
Rate — % (95% CI)		
6 mo	77.5 (71.7–82.3)	25.4 (18.0–33.6)
12 mo	63.0 (56.5–68.9)	10.5 (5.7–16.9)
18 mo	51.1 (43.3–58.3)	3.8 (1.1–9.2)
24 mo	44.3 (35.1–53.1)	NE
Prespecified sensitivity analyses		
Investigator assessment, ITT population — mo		
Median	16.6	3.7
95% CI	14.8–NE	3.5–5.4
IRR population — mo¶		
Median	16.6	3.6
95% CI	14.8–20.3	2.2–3.7
Secondary efficacy end points		
Overall survival, RPSFT adjusted, ITT population		
Median (95% CI) — mo	NE (22.0–NE)	NE (14.3–NE)
Rate, RPSFT adjusted — % (95% CI)		
6 mo	90.7 (86.4–93.7)	85.3 (78.0–90.4)
12 mo	81.6 (76.2–85.8)	70.0 (57.1–79.7)
18 mo	72.3 (65.7–77.9)	63.0 (44.3–76.9)
24 mo	58.2 (46.0–68.6)	NE
Response rate — no. (%)**	169 (64.8)	2 (1.5)
Complete response	4 (1.5)	0
Partial response	165 (63.2)	2 (1.5)
Stable disease	60 (23.0)	71 (54.2)
Durable stable disease ≥23 wk	40 (15.3)	39 (29.8)
Progressive disease	18 (6.9)	52 (39.7)
Could not be evaluated	14 (5.4)	6 (4.6)

nature medicine

Article

https://doi.org/10.1038/s41591-023-02321-8

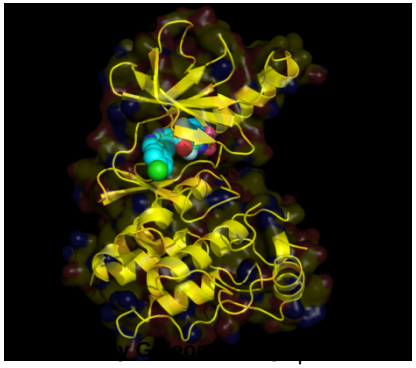
Dabrafenib plus trametinib in *BRAFV600E*-mutated rare cancers: the phase 2 ROAR trial

Table 2 | Best response and ORR in patient cohorts by investigator and independent radiology assessment

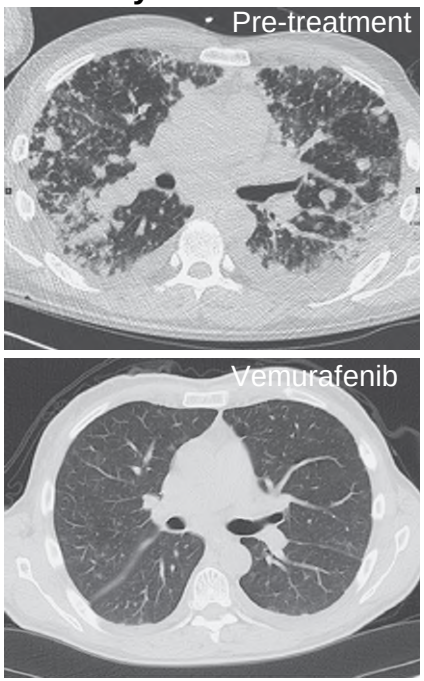
Cohorts	Investigator assessment						Independent radiology assessment					
	Best response						Best response					
	CR	PR	SD	PD	NE	RR	CR	PR	SD	PD	NE	RR
ATC (*n*=36)	3 (8%)	17 (47%)	11 (31%)	4 (11%)	1 (3%)[a]	20 (56%) (38.1%, 72.1%)	2 (6%)	17 (47%)	8 (22%)	8 (22%)	1 (3%)[a]	19 (53%) (35.5%, 69.6%)
BTC (*n*=43)	0	23 (53%)	16 (37%)	3 (7%)	1 (2%)[b]	23 (53%) (37.7%, 68.8%)	1 (2%)	19 (44%)	15 (35%)	6 (14%)	2 (5%)[c]	20 (47%) (31.2%, 62.3%)
ASI (*n*=3)	—	2 (67%)	—	1 (33%)	—	67% (9.4%, 99.2%)	—	2 (67%)	—	1 (33%)	—	67% (9.4%, 99.2%)
LGG (*n*=13)	1 (8%)	6 (46%)	3 (23%)	1 (8%)	0	7 (54%) (25.1%, 80.8%)	1 (8%)	6 (46%)	2 (15%)	0	3 (23%)[d]	7 (54%) (25.1%, 80.8%)
HGG (*n*=45)	3 (7%)	12 (27%)	10 (22%)	20 (44%)	0	15 (33%) (20.0%, 49.0%)	3 (7%)	11 (24%)	5 (11%)	21 (47%)	5 (11%)[e]	14 (31%) (18.2%, 46.6%)
HCL (*n*=55)	10 (18%) 26 (47%)[f]	13 (24%)	0	1 (2)	1 (2)[g]	49 (89%) (77.8%, 95.9%)	NA	NA	NA	NA	NA	NA
MM (*n*=10)	0[h]	2 (20%)[i]	1 (10%)	4 (40%)	0	5 (50%) (18.7%, 81.3%)	NA	NA	NA	NA	NA	NA

Vivek Subbiah, Robert J. Kreitman, Zev A. Wainberg, Anas Gazzah, Ulrik Lassen, Alexander Stein, Patrick Y. Wen, Sascha Dietrich, Maja J. A. de Jonge, Jean-Yves Blay, Antoine Italiano, Kan Yonemori, Daniel C. Cho, Filip Y. F. L. de Vos, Philippe Moreau, Elena Elez Fernandez, Jan H. M. Schellens, Christoph C. Zielinski, Suman Redhu, Aislyn Boran, Vanessa Q. Passos, Palanichamy Ilankumaran & Yung-Jue Bang

Targeting BRAF^{V600E} by the first FDA-approved orally available selective inhibitor

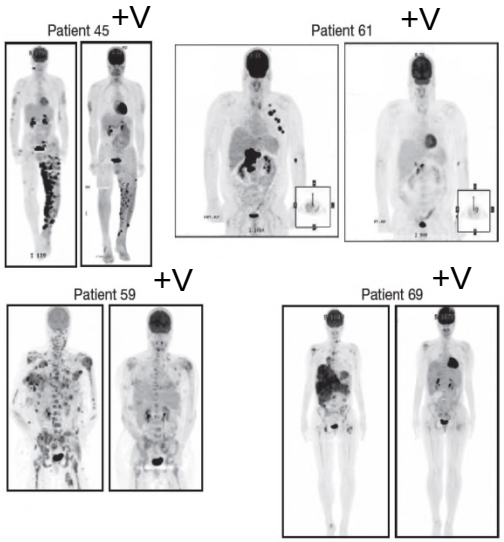


Patient with Anaplastic Thyroid Cancer



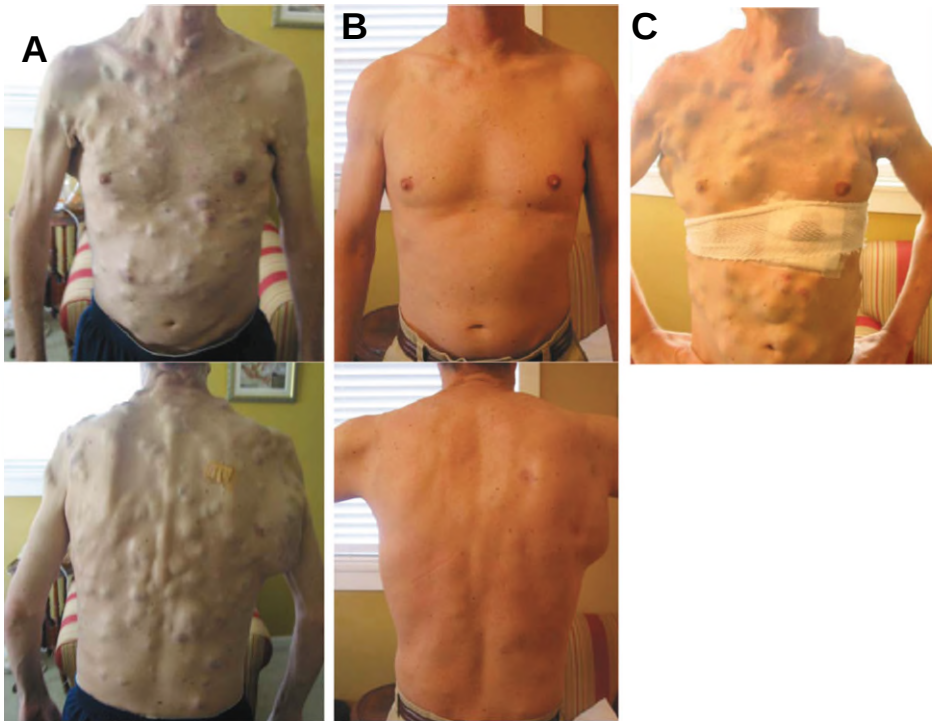
Rosove MH et al. NEJM 2013

Patients with Melanoma



Bollag G. et al. Nature 2010

Drug resistance: recurrence in patients with BRAF^{V600E}-melanoma



Wagle N. et al., JCO 2011

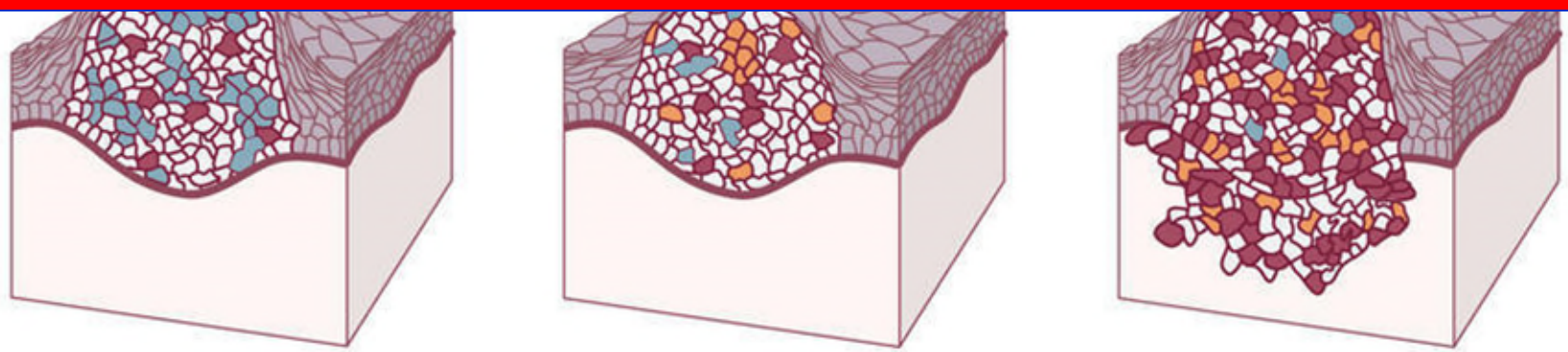
Disease progression and death

WHAT IS DRUG RESISTANCE?

Drug resistance is a major cause of cancer treatment failure. While a treatment may be effective initially, the heterogeneity of cancer and its ability to adapt can allow the cancer to become resistant to the treatment and regrow. Solving the puzzle of why this happens and how to overcome or prevent it is a goal that NCI is pursuing on many fronts, including basic science to understand biological mechanisms and clinical trials testing new treatment strategies.

Ongoing dynamic risk of stratification: Incomplete Structural Response to Therapy

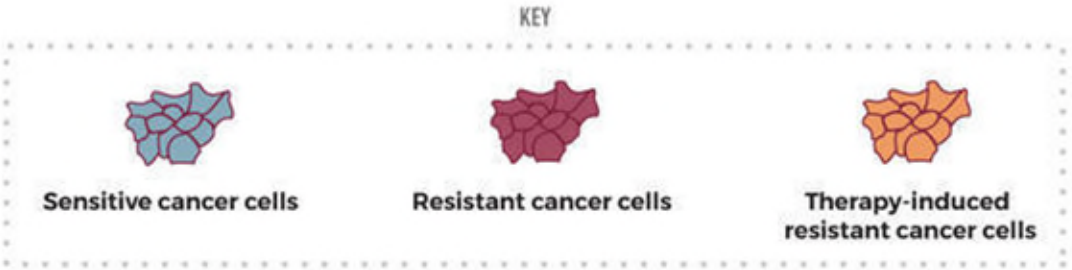
Tuttle M, Thyroid 2011



Before Treatment
Tumors consist of cancer cells with different molecular features, which may make them sensitive or resistant to different types of treatments.

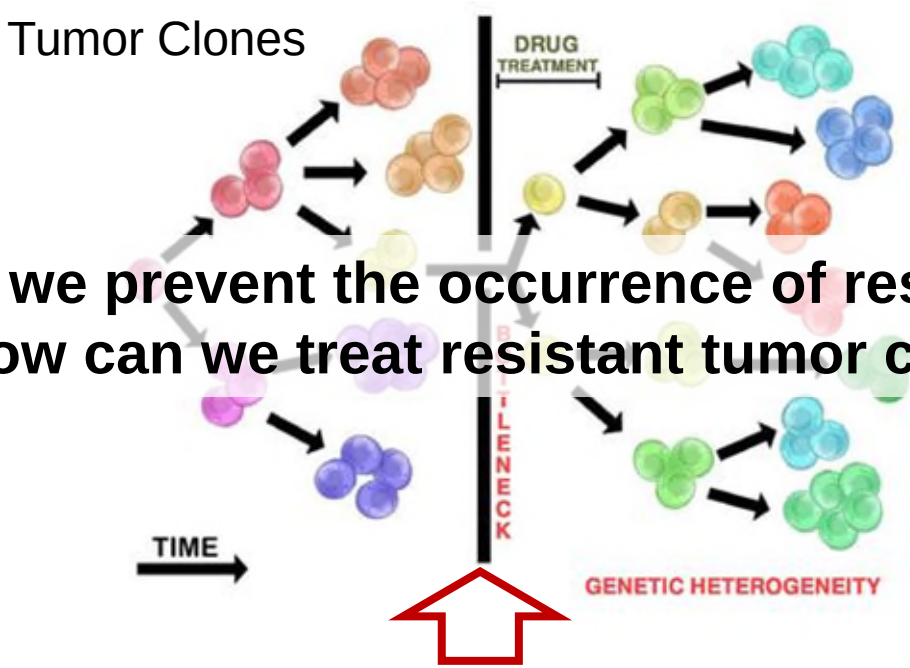
Responding to Treatment
Although, a drug may kill some cancer cells (the sensitive cells), a subset of them almost invariably survives (the resistant cells).

Developing Drug Resistance
The cancer cells that are resistant will multiply, contributing to the re-growth of the tumor.



cancer.gov

Cell heterogeneity within tumors can be considered a substrate for evolutionary adaptation to the environment *via* Darwinian selection

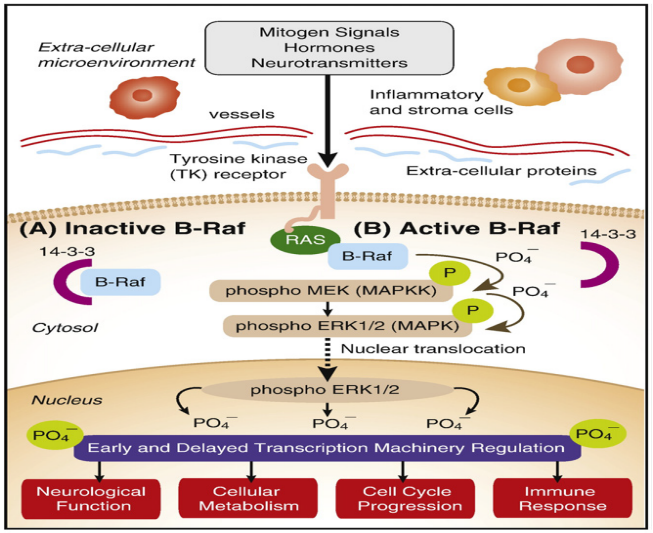


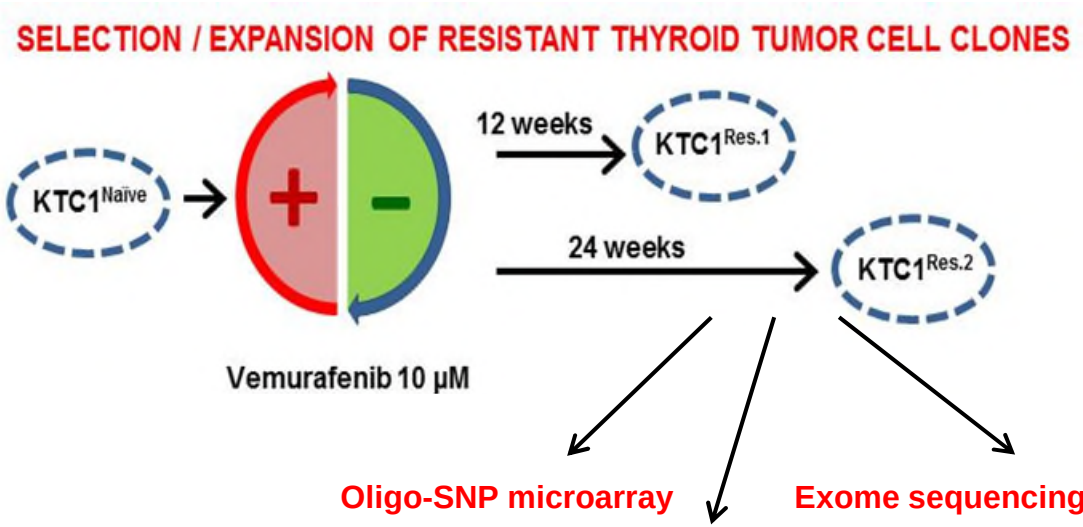
1. How can we prevent the occurrence of resistant tumor cells?
2. How can we treat resistant tumor cells?

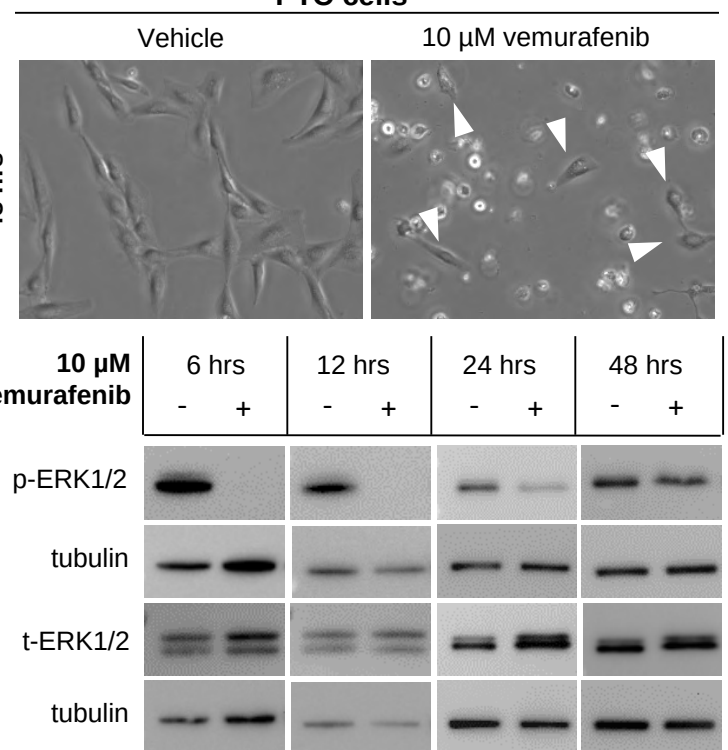
$BRAF^{V600E}$ and tyrosine kinase (TK) inhibitors (bottleneck)

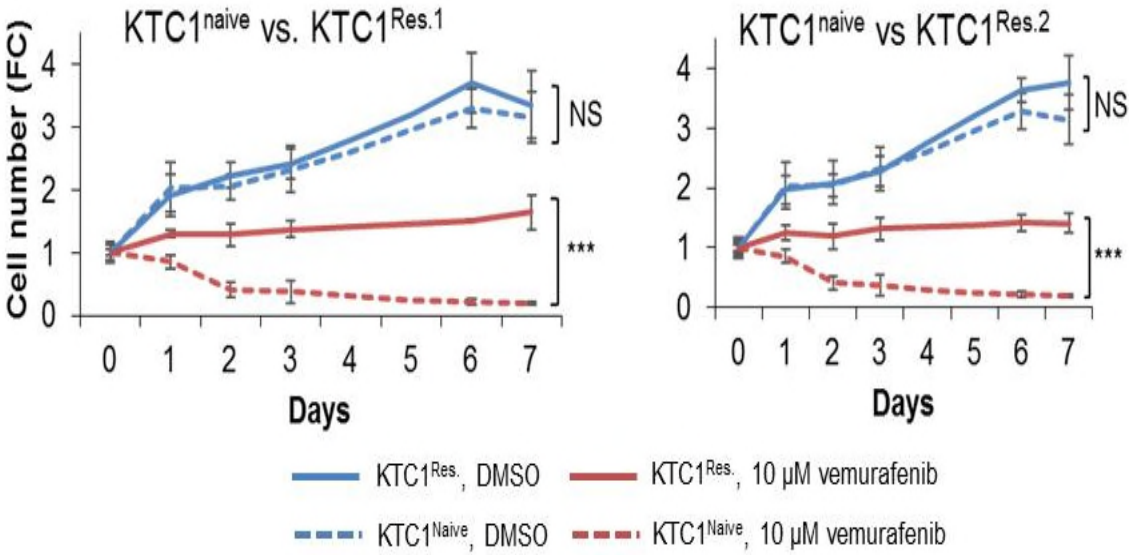
Tumor resistance and relapse are the outcome of an evolution process driven by a major selective pressure

Model of resistance to vemurafenib in metastatic PDTC patient-derived cells with BRAF$^{WT/V600E}$ mutation and P16 (CDKN2A) deletion



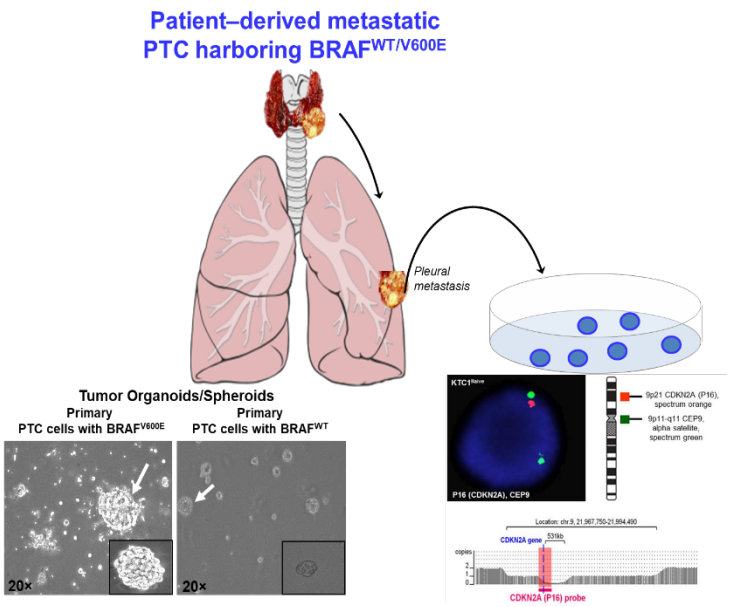


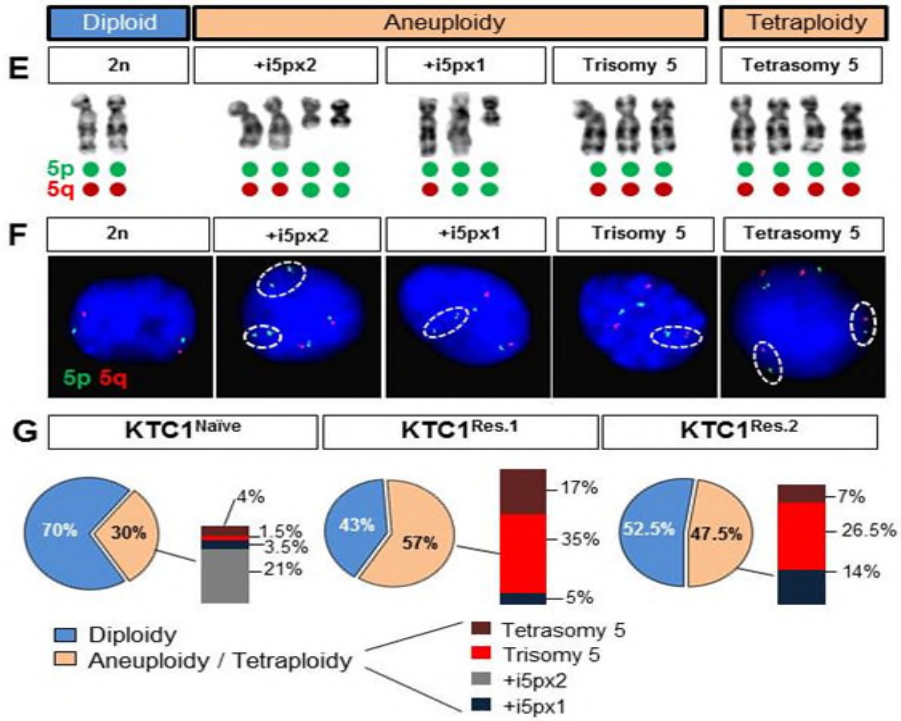




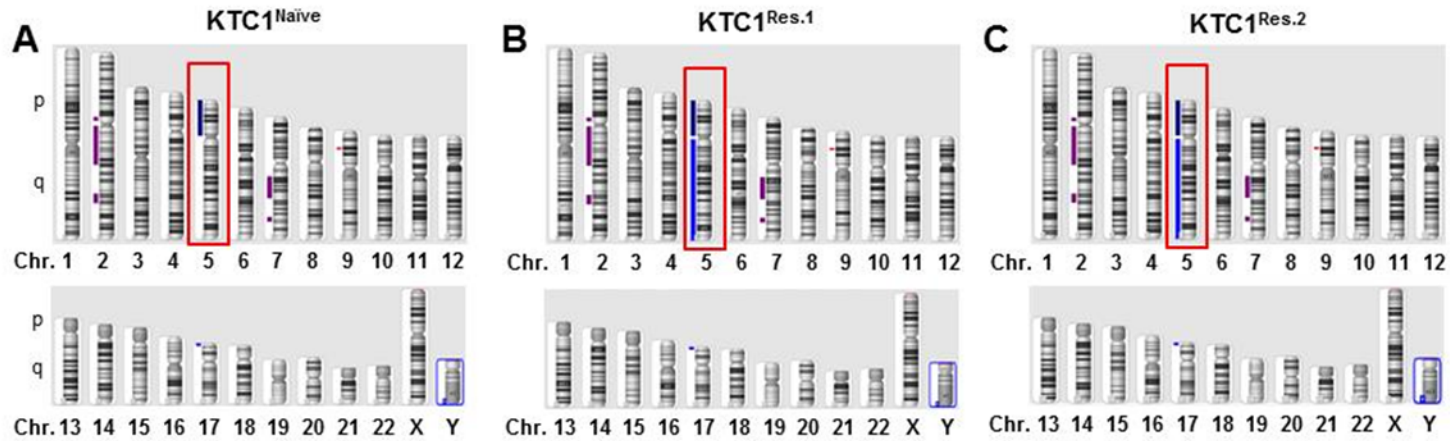
Antonello Z…et al and Nucera C. et al.

Resistance to BRAF^{V600E} inhibitor triggers an increased tetraploidy/aneuploidy and expansion of clones with chr.5 amplification





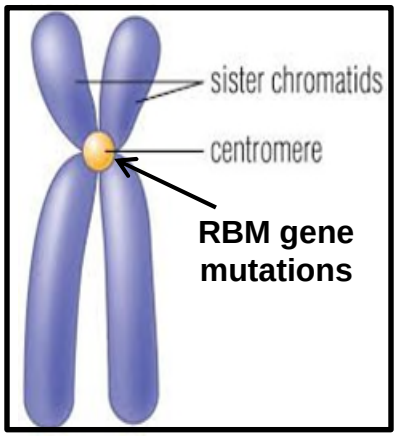
Antonello Z…et al and Nucera C. et al. Oncotarget



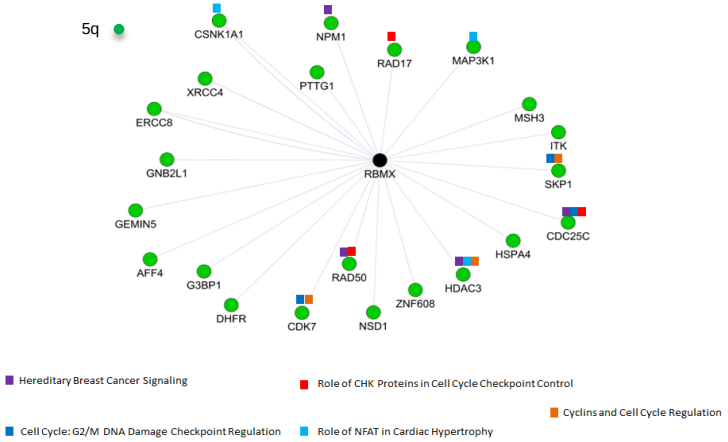
Vemurafenib-resistant $BRAF^{V600E}$-PDTC patient-derived cells acquire *de novo* mutations in RBM genes which contribute to DNA tetraploidy

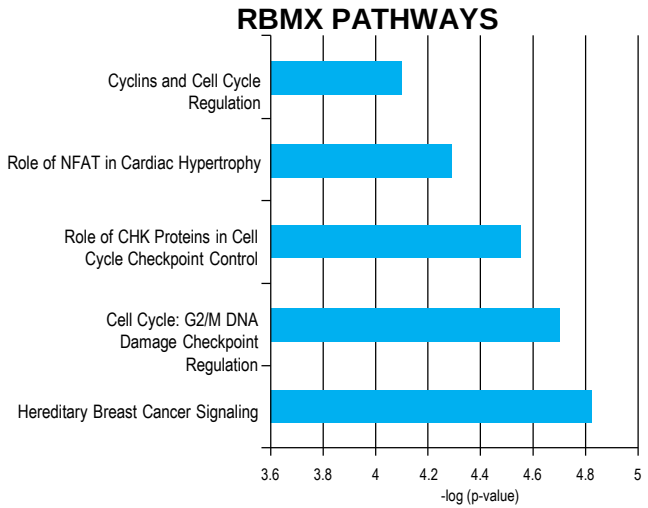
RBM10 gene
(chromosome X, 1537_1539delGAG, E513del)

RBMX gene
(chromosome X, 499C>G, P167A)



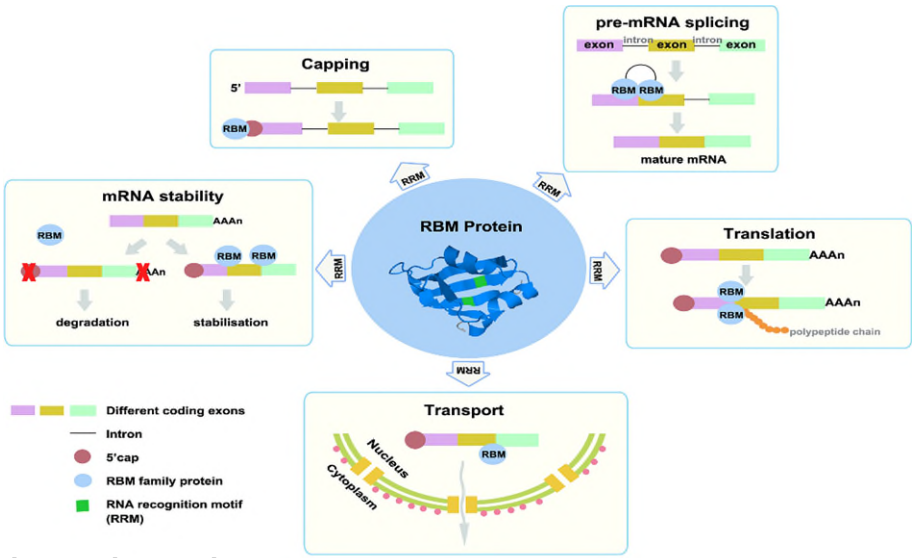
RBMX gene regulatory networks on chr.5q



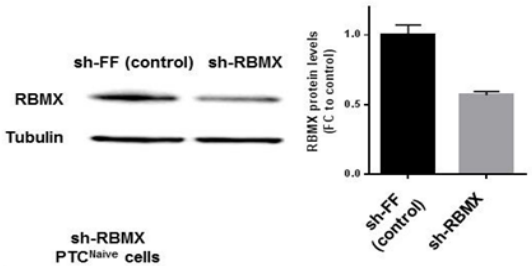


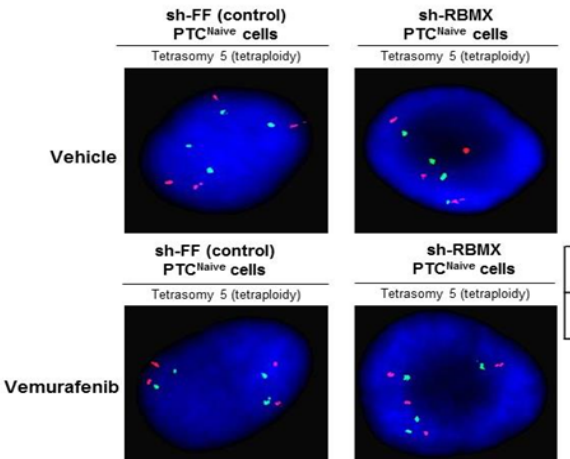
Antonello Z..., and Nucera

The RNA-binding motif (RBM) proteins



Li Z. et al. Frontiers 2021

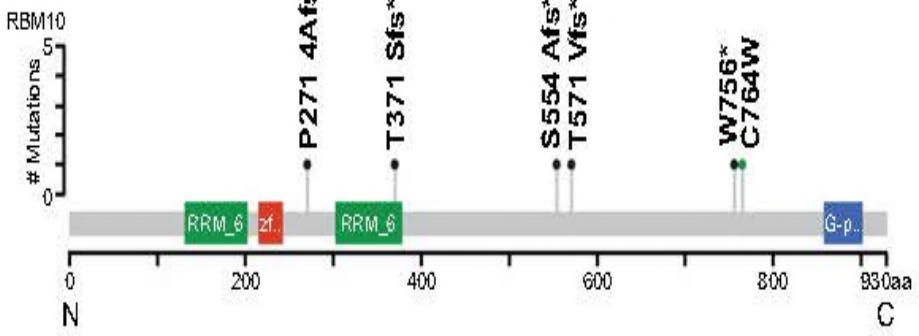


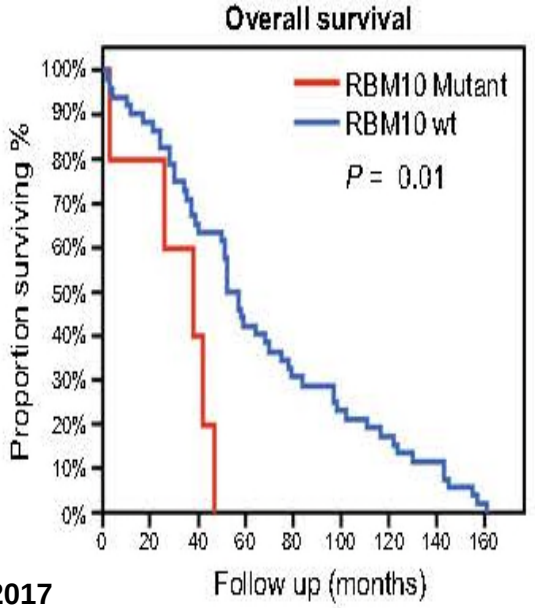


	Tetrasomy 5 (due to tetraploidy)	
	sh-FF (control) PTC^{Naive} cells	sh-RBMX PTC^{Naive} cells
Vehicle	9.5%	11.5%
Vemurafenib	7.5%	19.5%

$p<0.05$

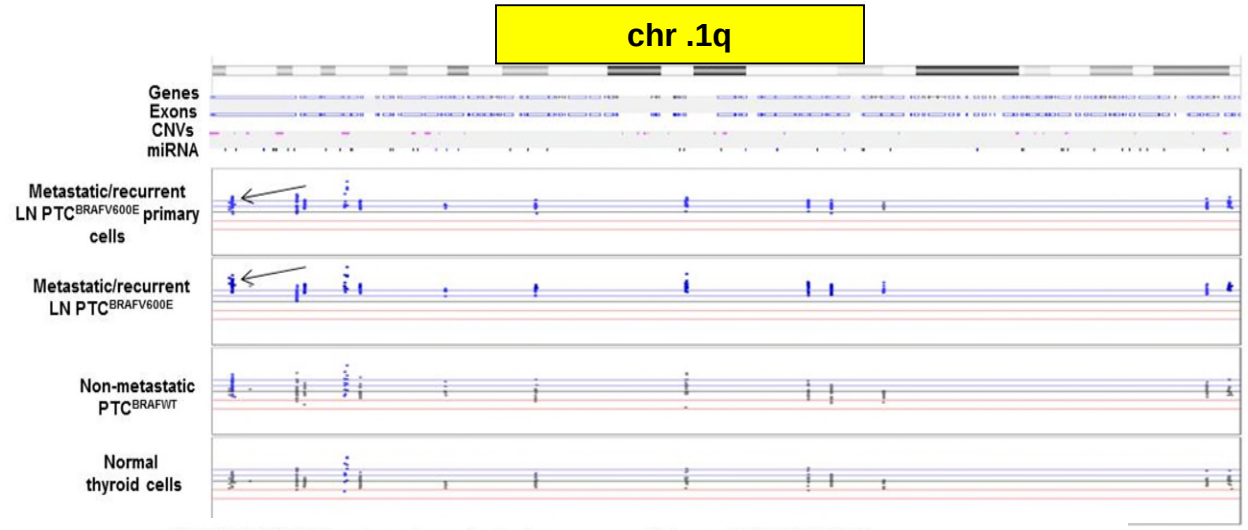
RBM mutations affect overall survival in aggressive non-anaplastic thyroid cancer

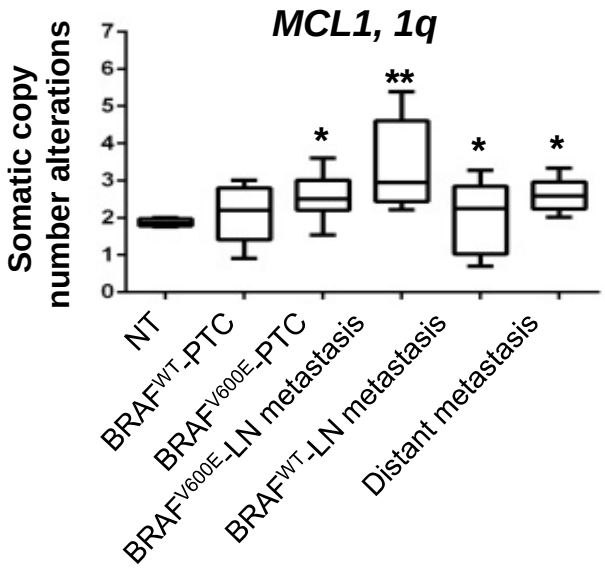


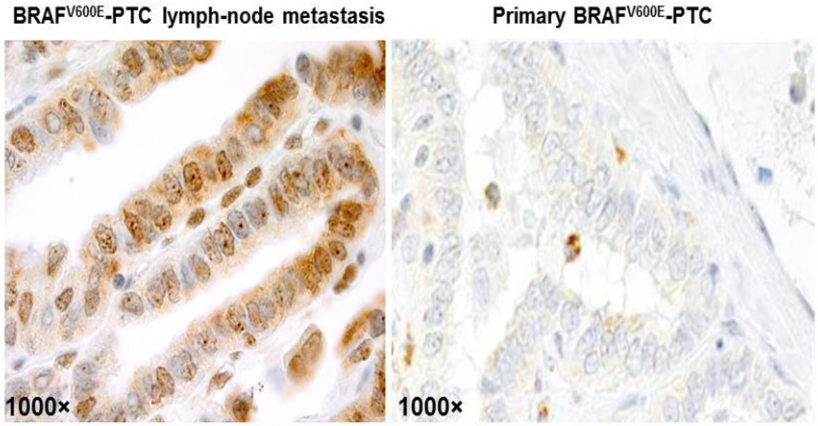


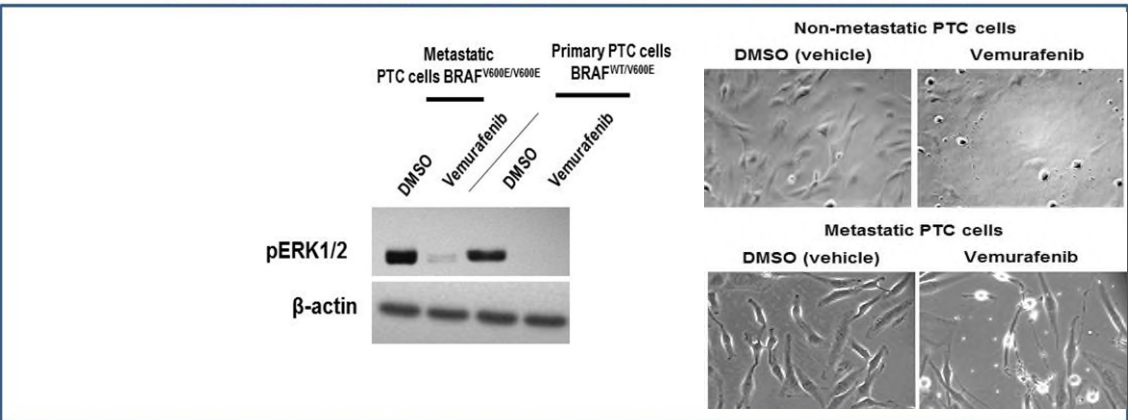
Ibrahimpasic T. et al. and Ian G., Clin. Cancer Res. 2017

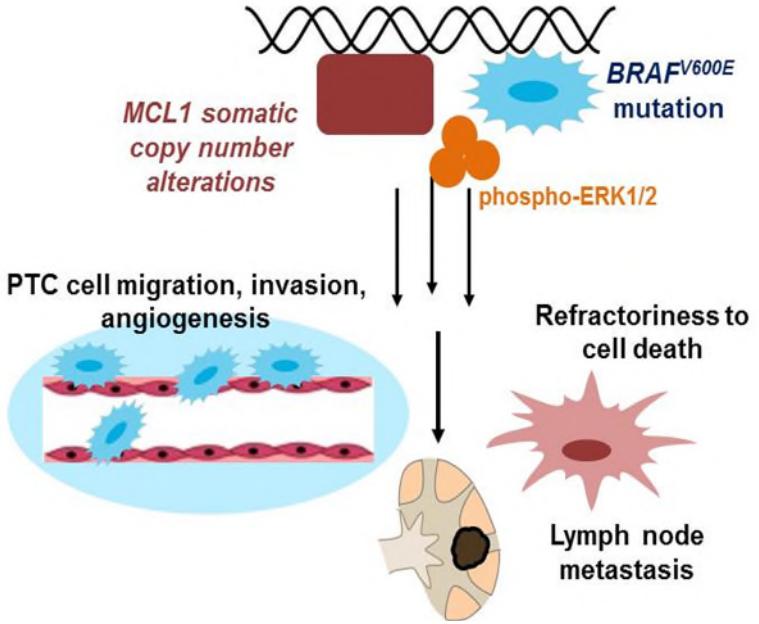
MCL1 (chr.1q) somatic copy number alterations (SCNAs) in metastatic PTC samples











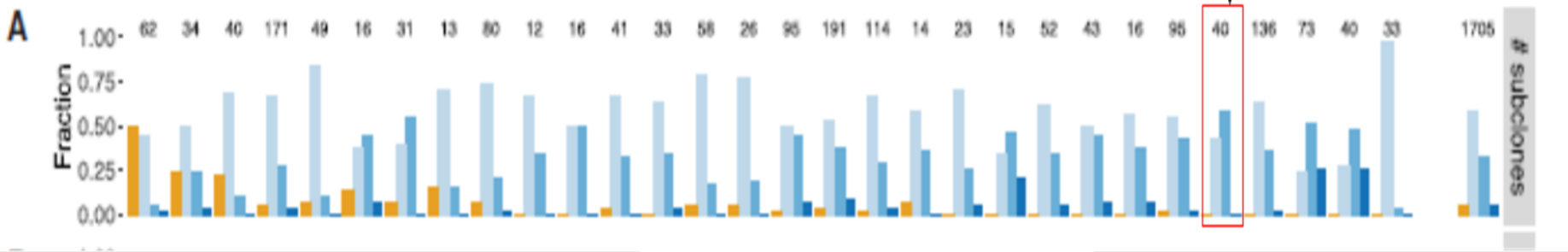
Duquette M, et al...and Nucera C. Oncotarget

Cell
Resource

Genetic intra-tumor heterogeneity across 2,658 human cancer genomes

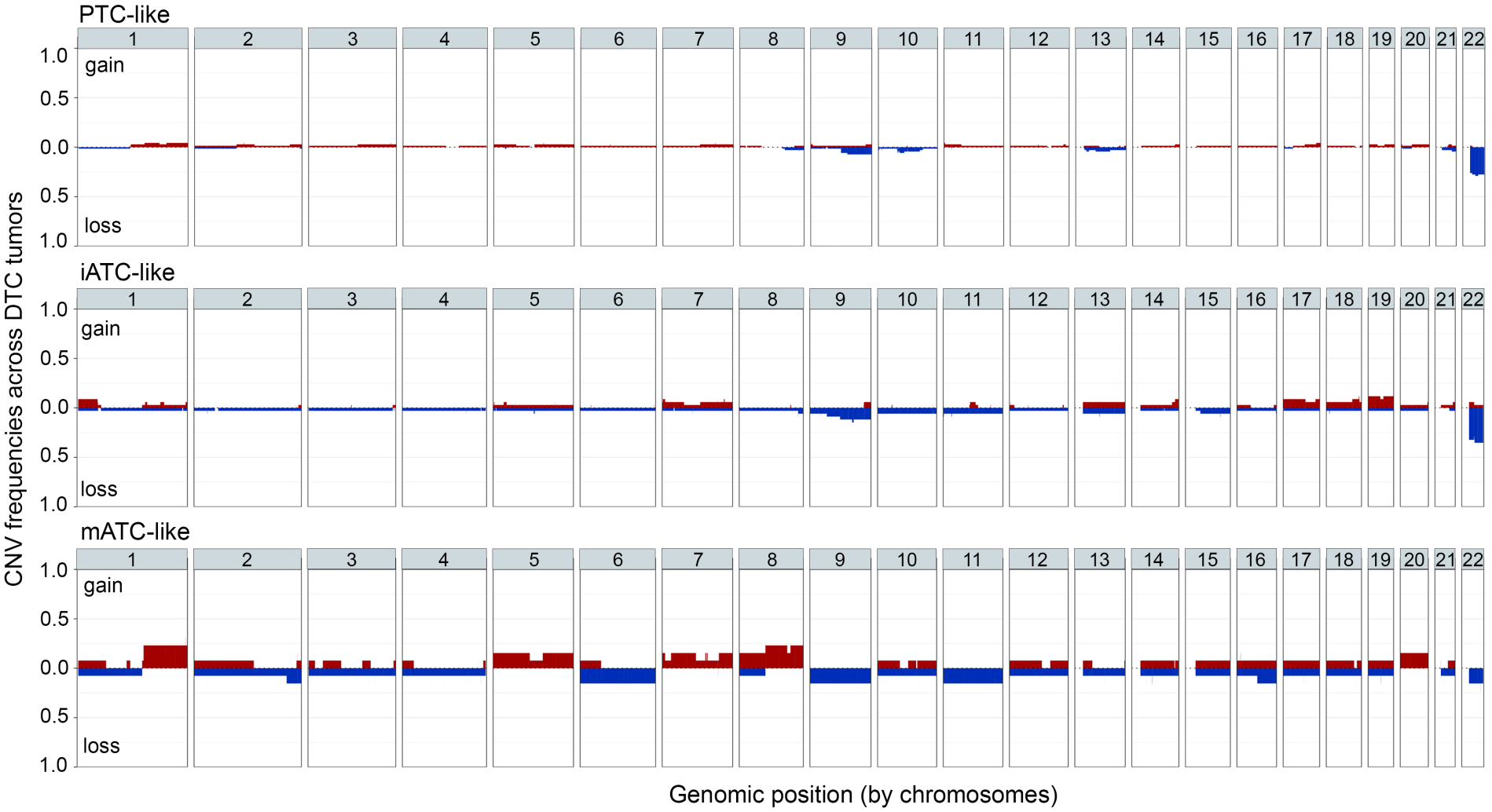
ThyCa

CellPress
OPEN ACCESS



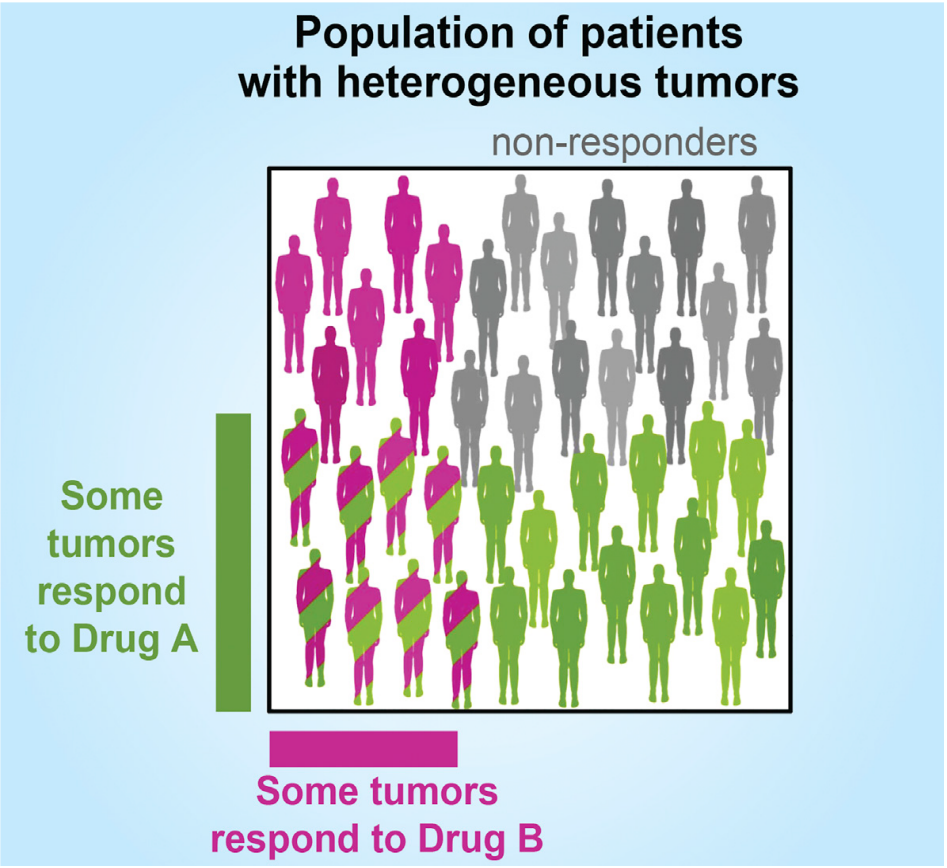
PCAWG Consortium, Cell 2021

ATC-like DTC harbored aneuploid tumor cells with high-magnitude copy-number



Lu L. et al., JCI 2023

Combination cancer therapy can confer benefit via patient-to-patient variability



Highlights:

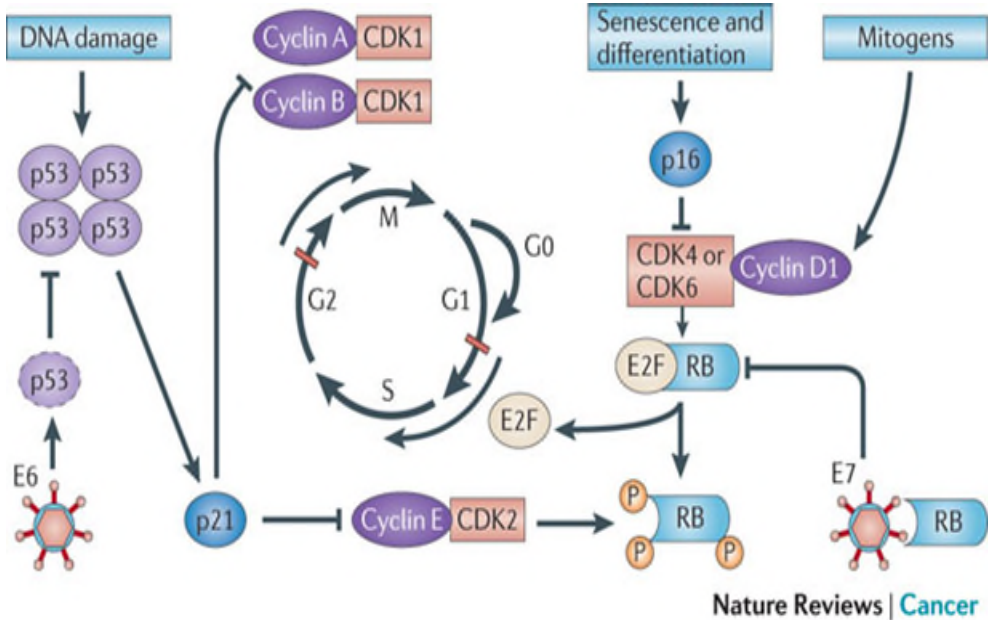
Anti-cancer drugs have variable efficacy within patient populations.

Drug combinations give each patient more chances that one drug could be effective.

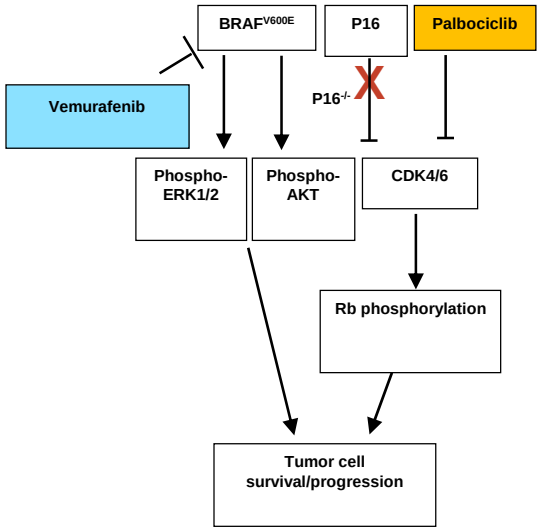
Optimizing combined therapies represents a fundamental approach to design cancer treatments.

Cell 2017

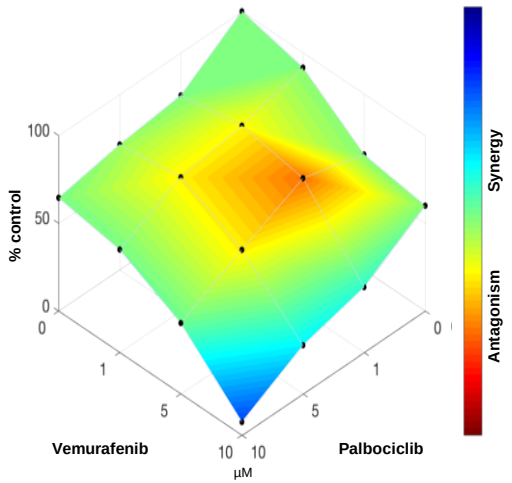
Combined therapy with BRAF^{V600E} and cell cycle inhibitor in metastatic lung pleural effusions PDTC patient-derived cells



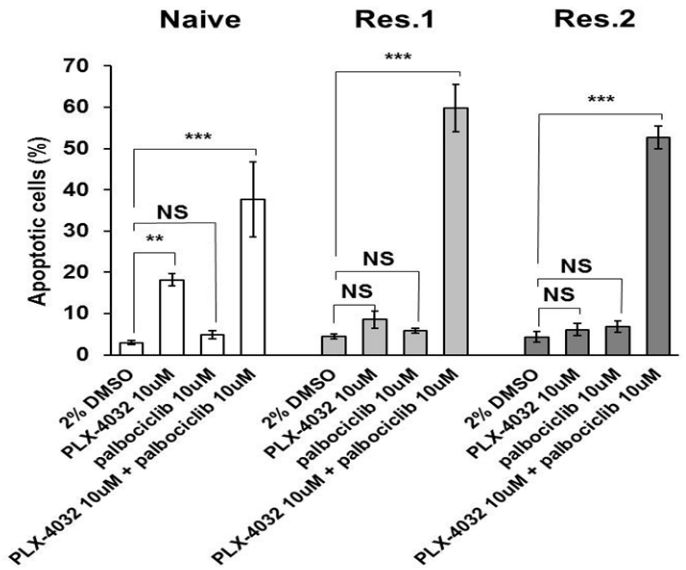
Therapeutic approach



Combined therapy assay



Cell death assay

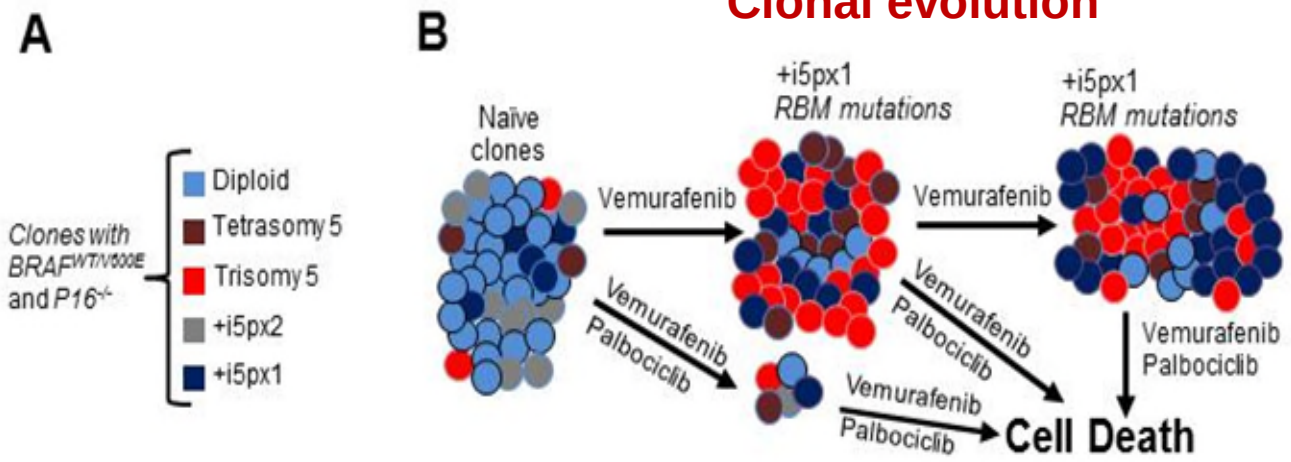


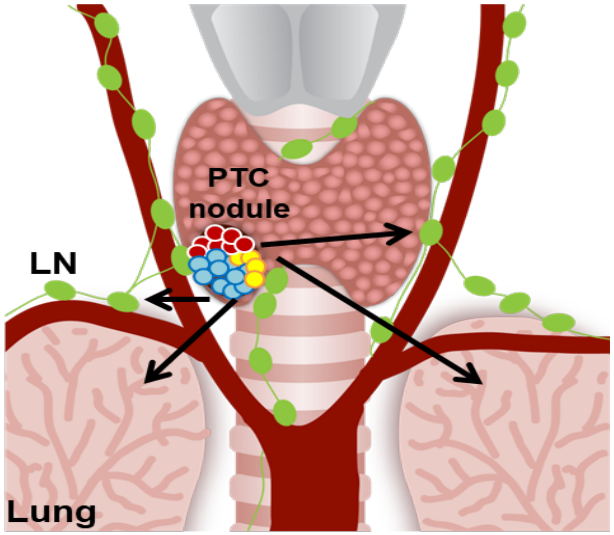
Antonello Z…et al and Nucera C. et al. Oncotarget

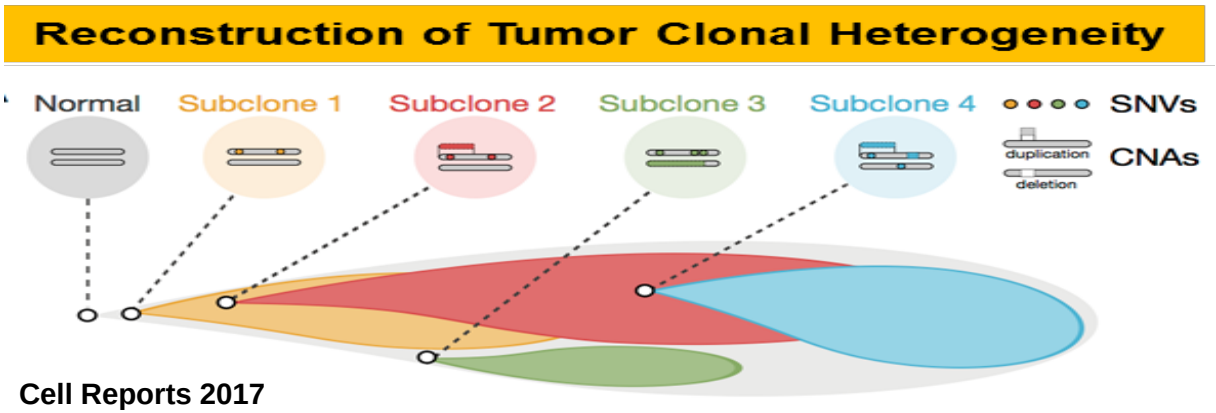
Take-home messages

Combined therapy represents a novel therapeutic strategy for $BRAF^{V600E}$ thyroid cancer by preventing selection and expansion of aggressive cell clones with somatic copy number alterations (SCNAs).

Clonal evolution



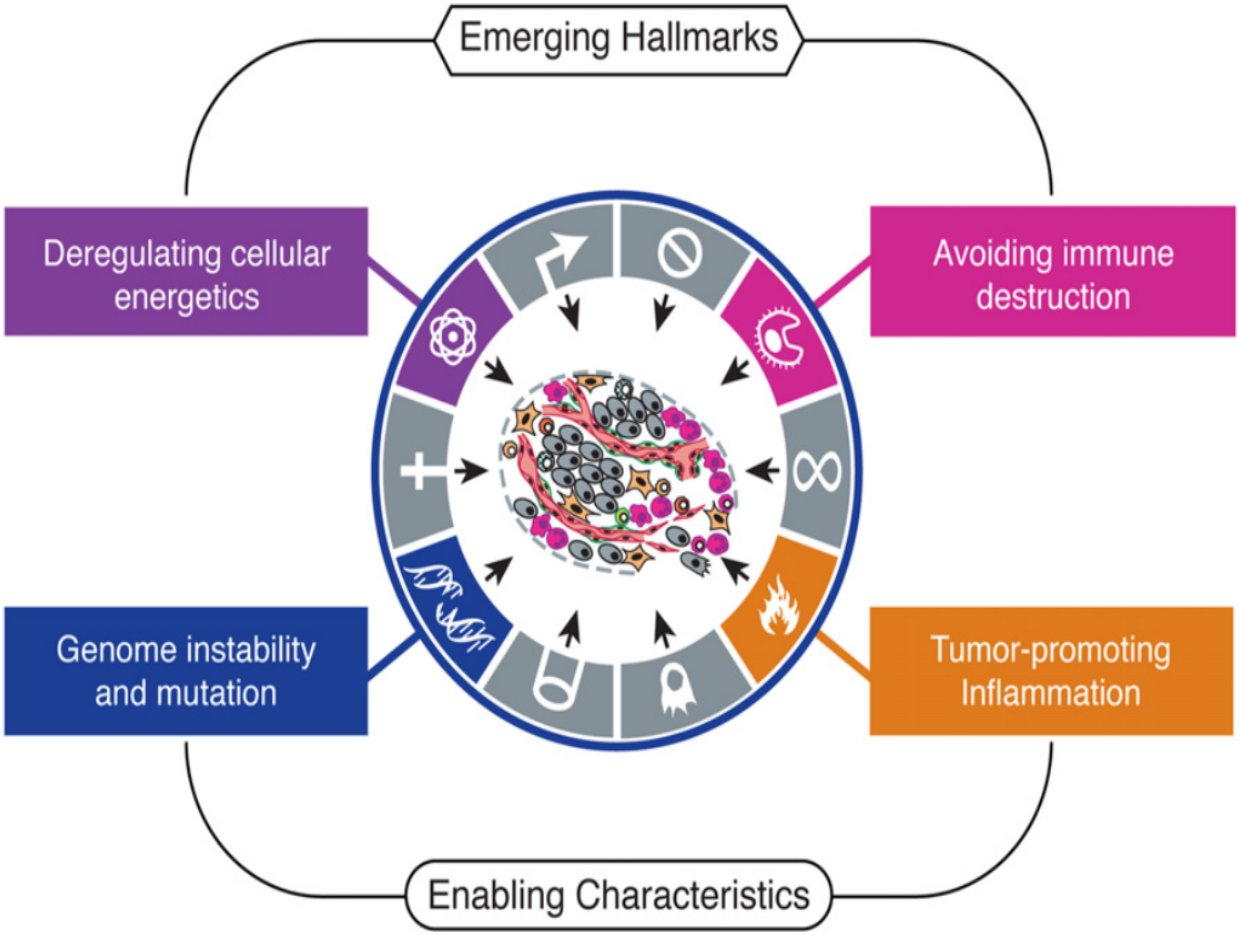




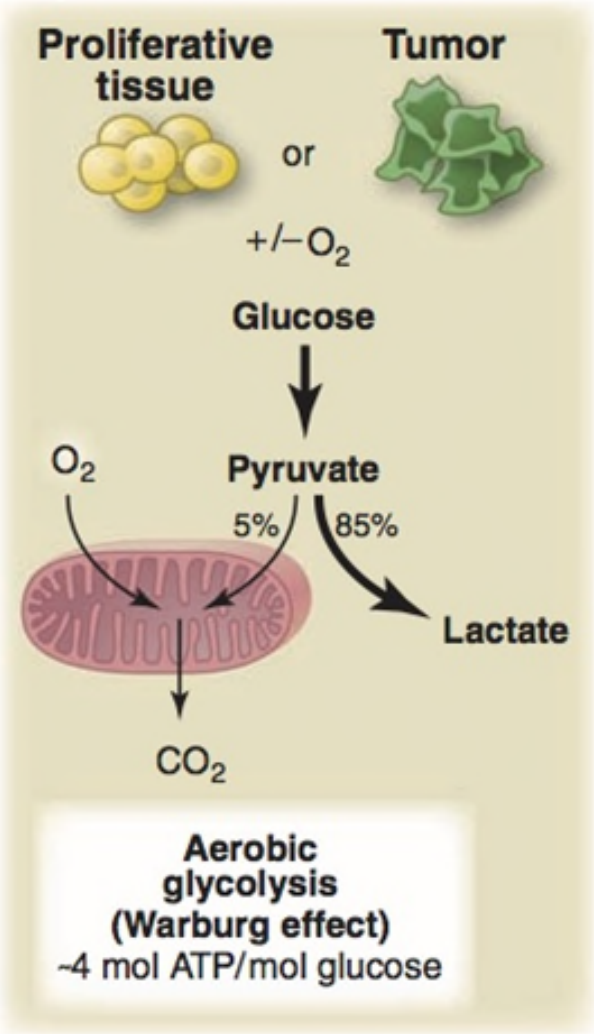
Cell Reports 2017

Cell metabolism/energy alterations provide insights for new therapeutic strategies

Coding Genes for Thyroid Cancer Metabolism

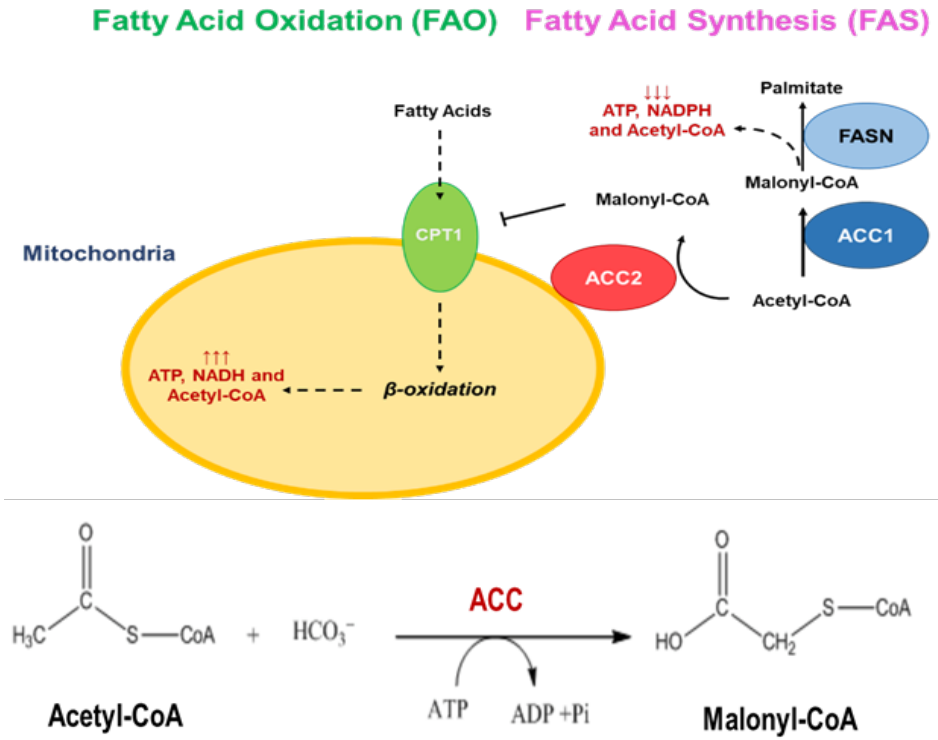


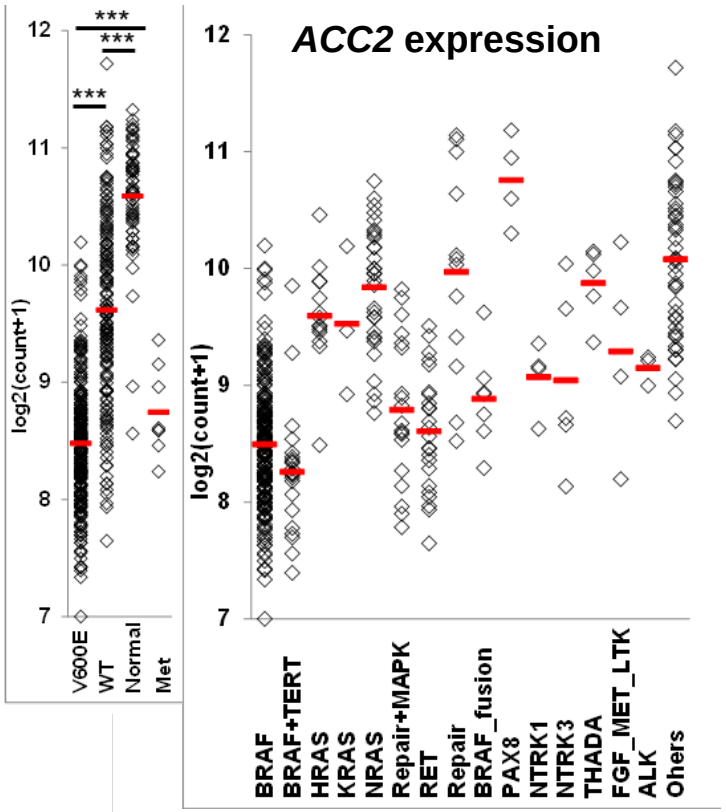
Hanahan D and Weinberg RA. Cell, 2011

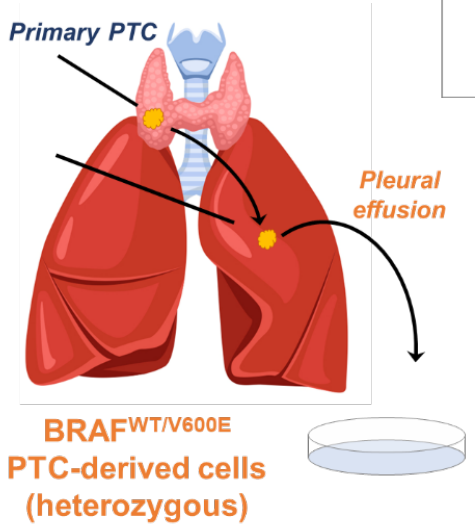


Adapted from Vander Heiden, MG , Cantley, LC.&Thompson, CB Science, 2009

Fine-tuning lipid metabolism by targeting mitochondria-associated Acetyl-CoA-Carboxylase-2 (ACC2) in metastatic BRAF^{V600E} PTC

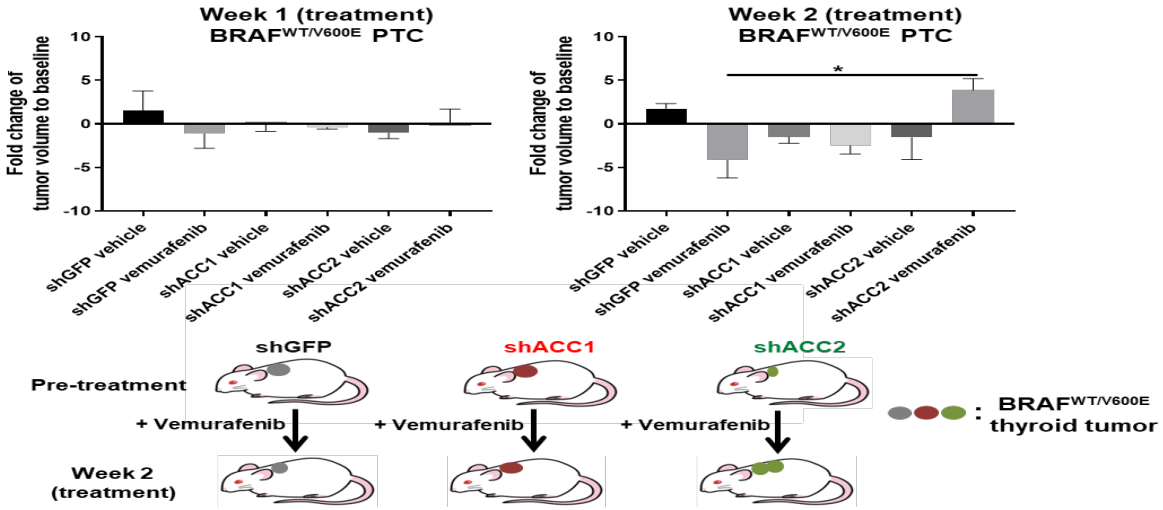


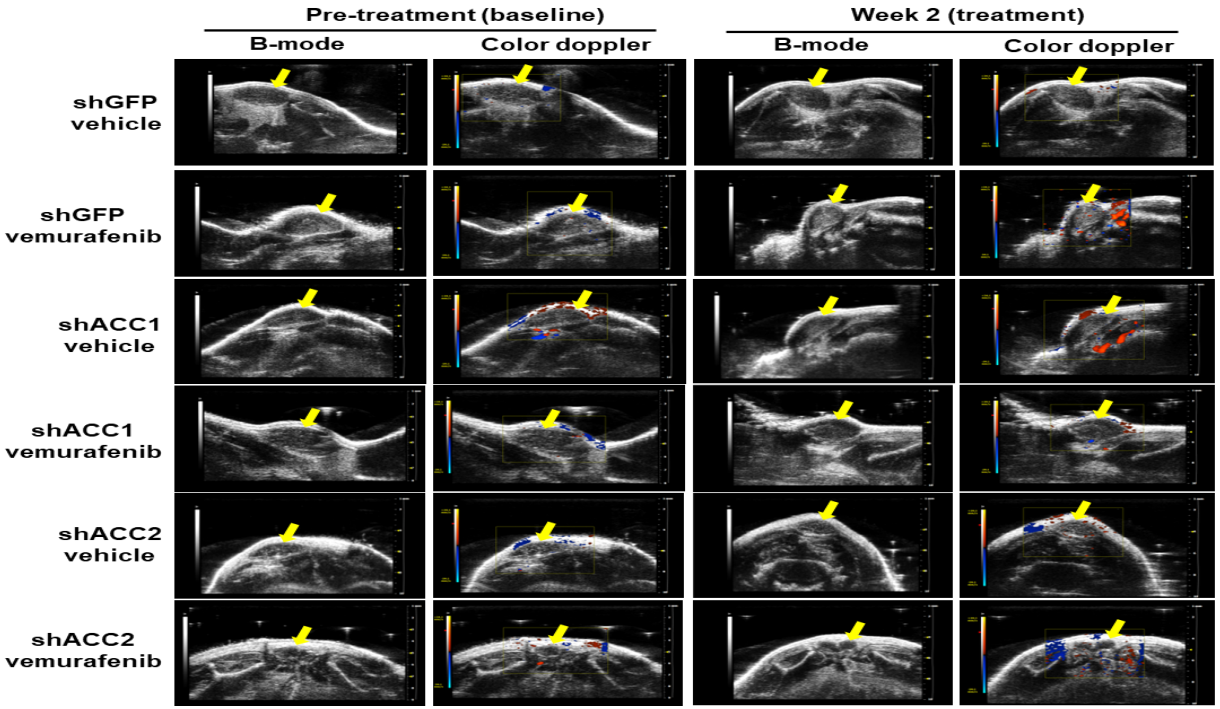




Valvo V…and Nucera C. Thyroid 2021

ACC2 knockdown contributes to resistance to vemurafenib therapy in a xenograft mouse model derived from metastatic BRAF$^{WT/V600E}$ PTC-derived cells, leading to increased tumor cell growth





Valvo V…and Nucera C. Thyroid 2021

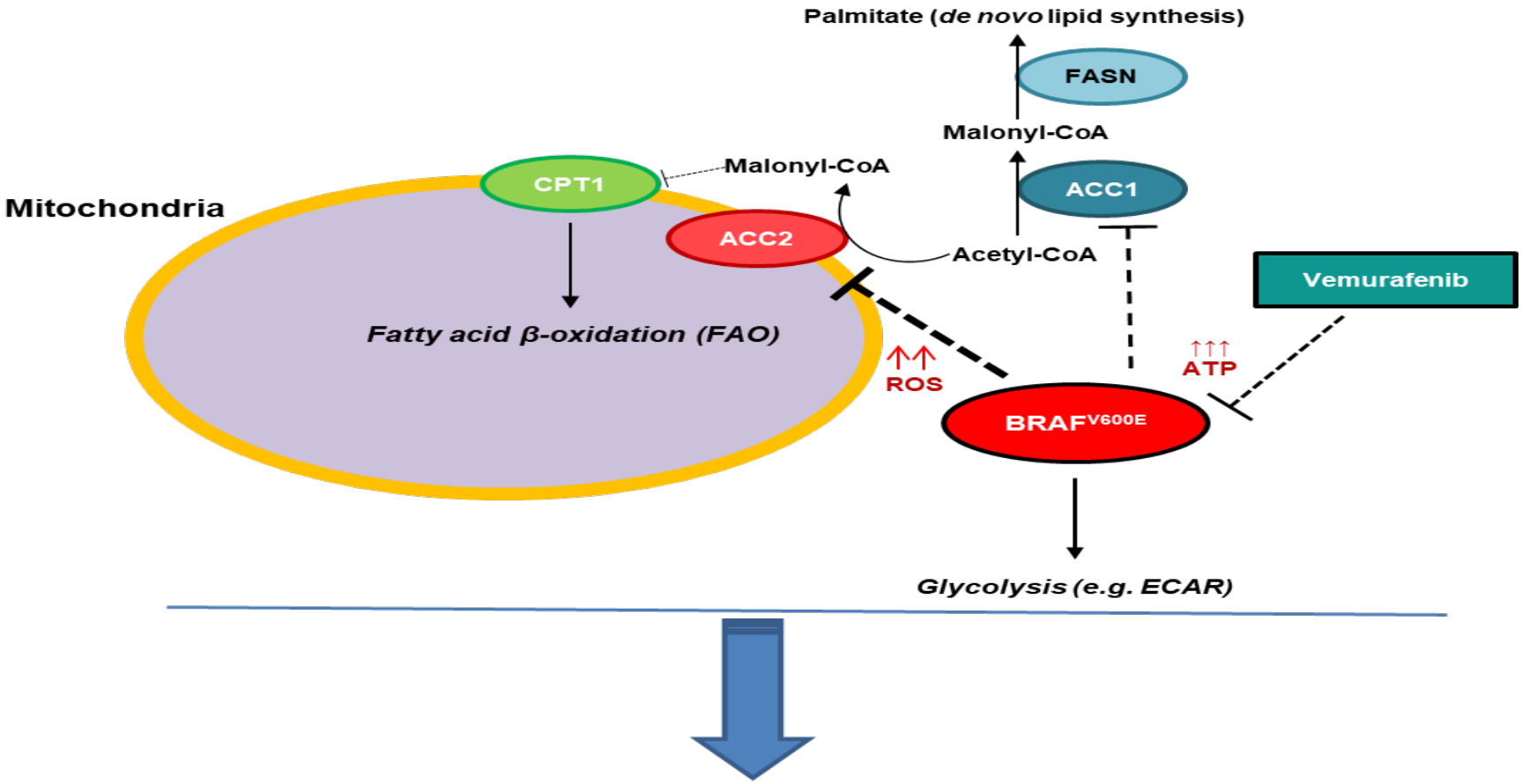
Translational Significance

These findings indicate a link between $BRAF^{V600E}$ and lipid metabolism regulation in PTC.

$BRAF^{V600E}$ down-regulates ACC2 levels, which deregulates *de novo* lipid synthesis and FAO, leading to drug resistance and tumor growth.

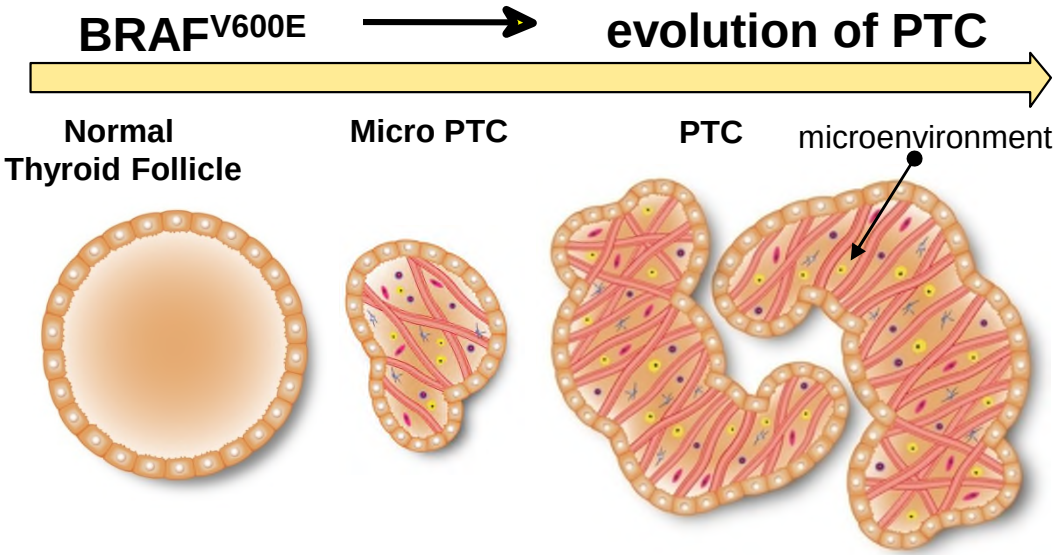
ACC2 rescue may represent a novel molecular strategy overcoming resistance to $BRAF^{V600E}$ inhibitors in refractory PTC

Experimental metabolic model of *ACC* genes' functions for thyroid carcinoma cell growth

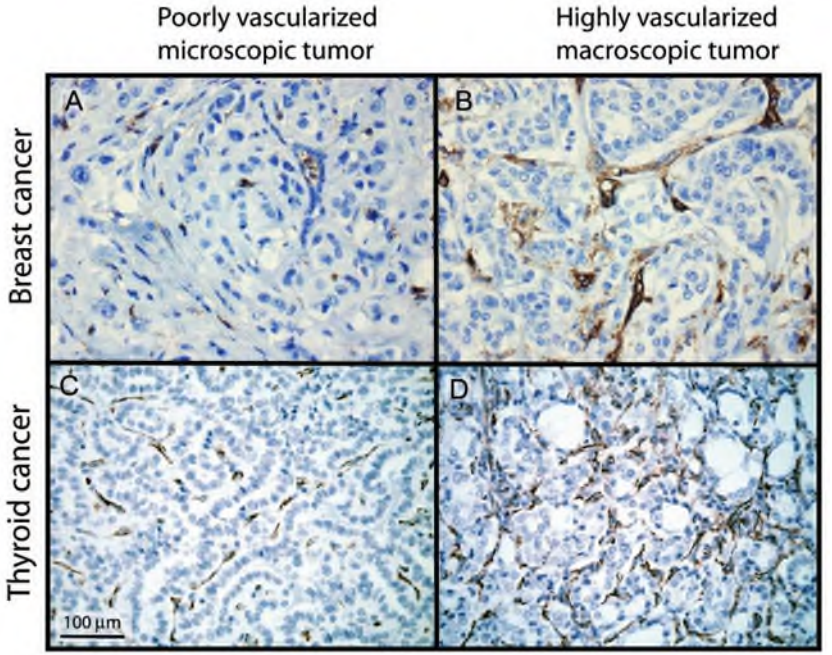


Valvo V…and Nucera C. Thyroid 2021

Thyroid Cancer angiogenic microenvironment and dormancy

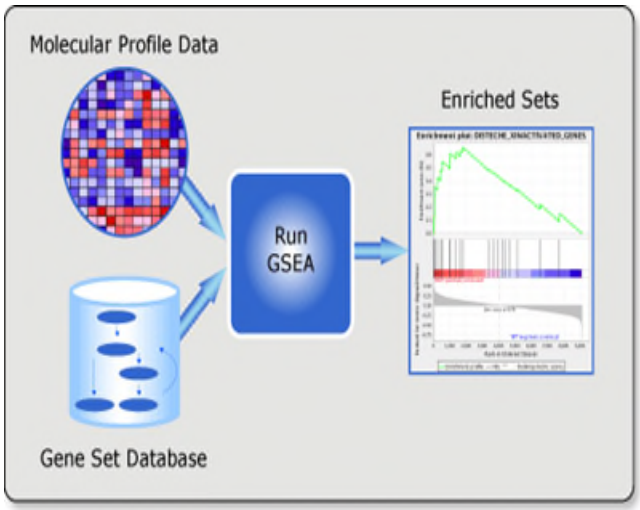


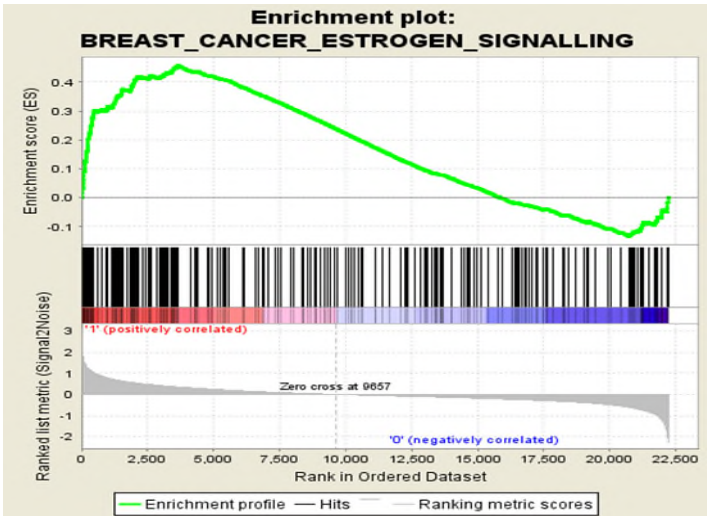
Nucera C., Frontiers in Cancer Endocrinology



Naumov G., Akslen L. and Folkman J., 2006

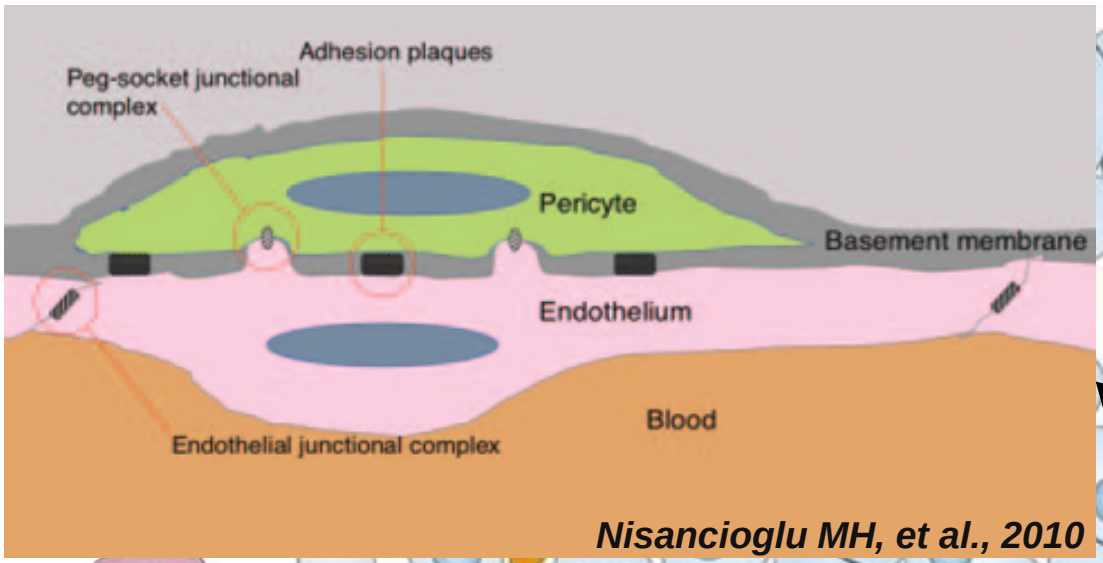
BRAF^{V600E}-PTC and Microenvironment Gene Set Signature





Nucera C. et al., PNAS 2010

Tumor microenvironment is crucial to elicit resistance to targeted therapy

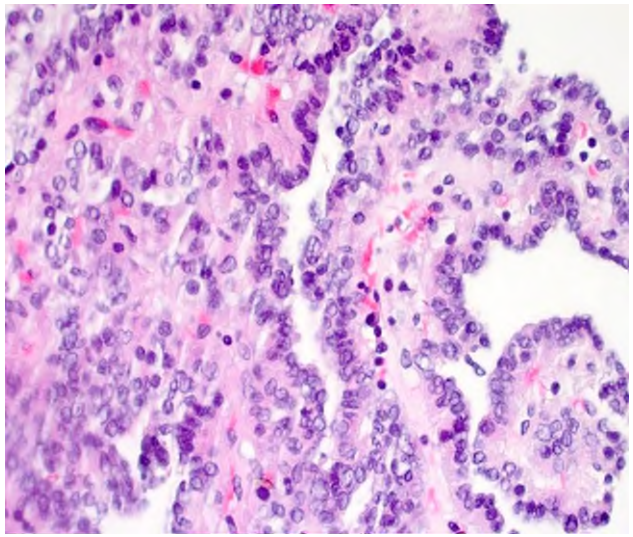


Nisancioglu MH, et al., 2010

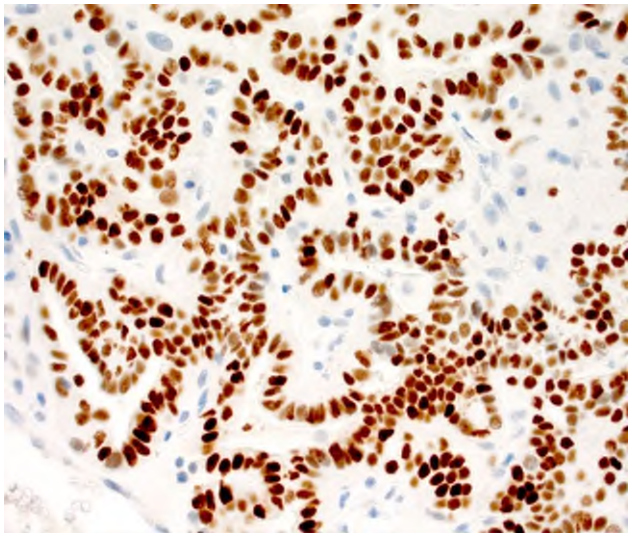
Egeblad M, Nature Reviews Cancer

Pericytes are enriched in the PTC microenvironment

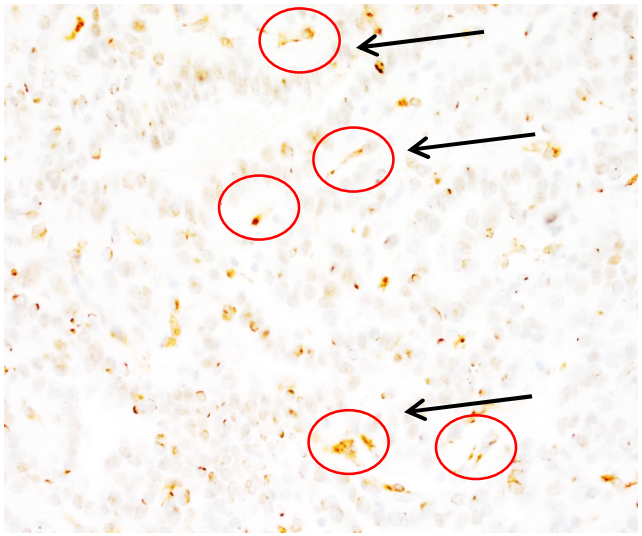
Metastatic PTC, H&E



PTC cells, PAX8+

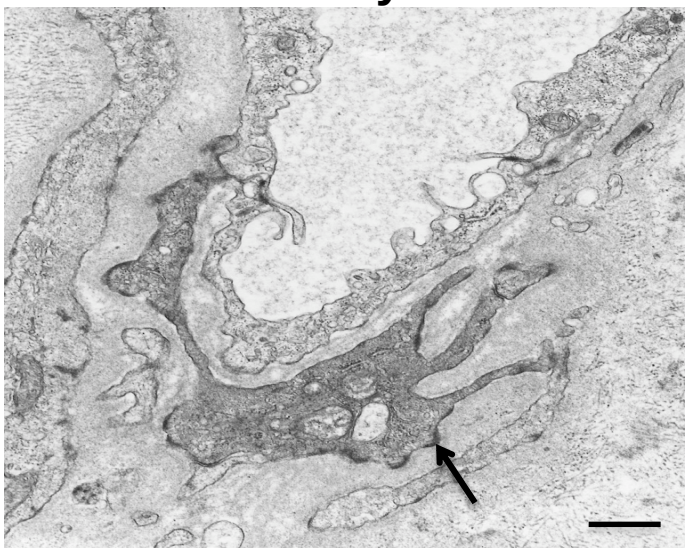


PTC cells and pericytes, PDGFRB+

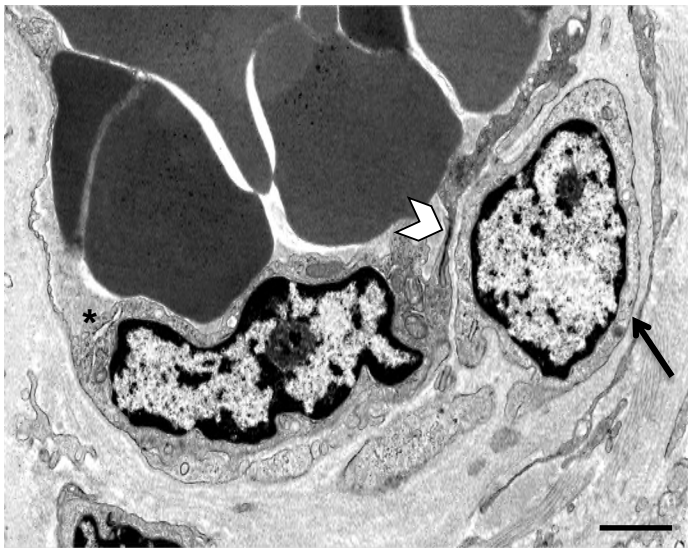


Electron Microscopy

Normal Thyroid

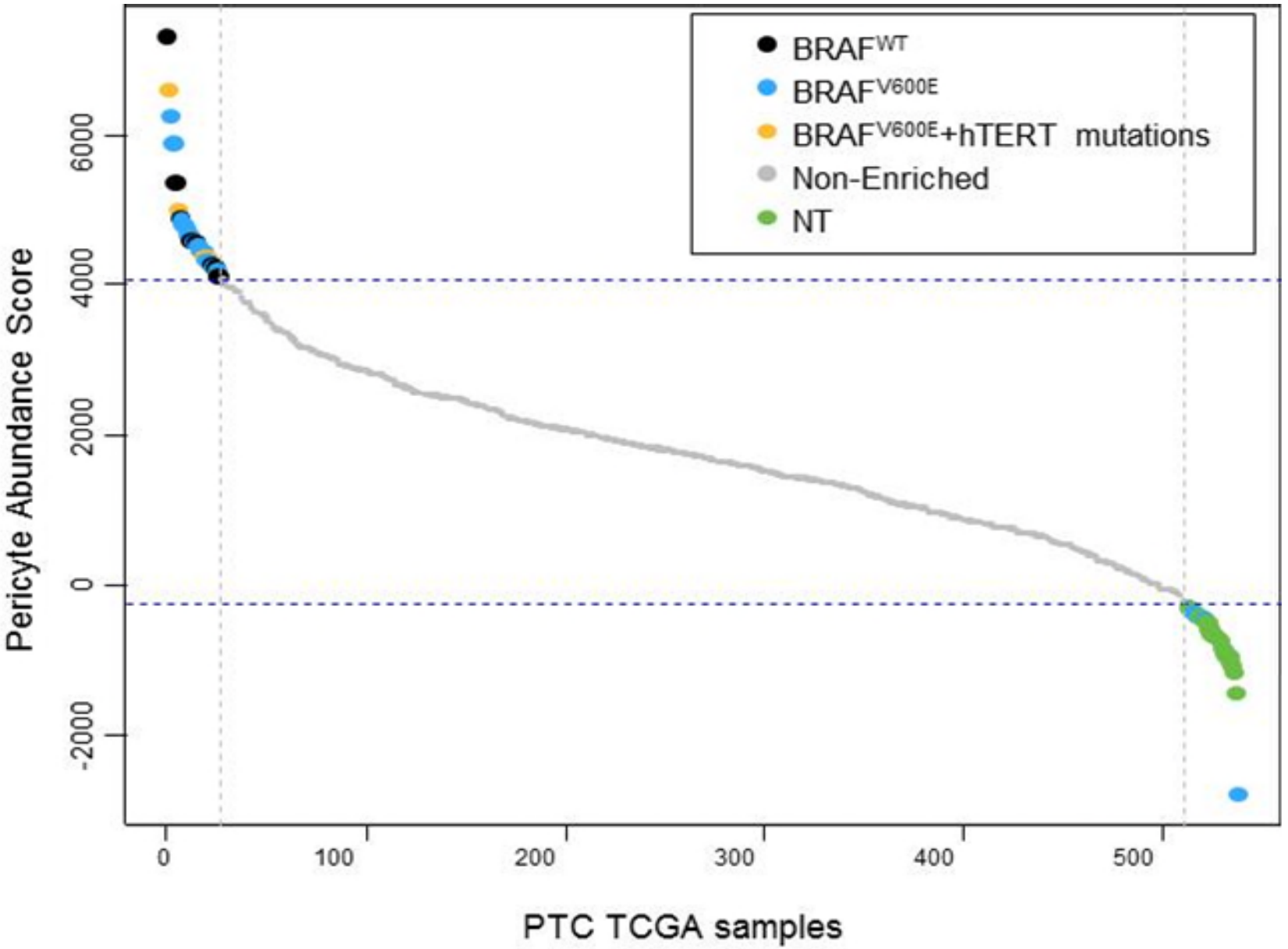


Thyroid Cancer



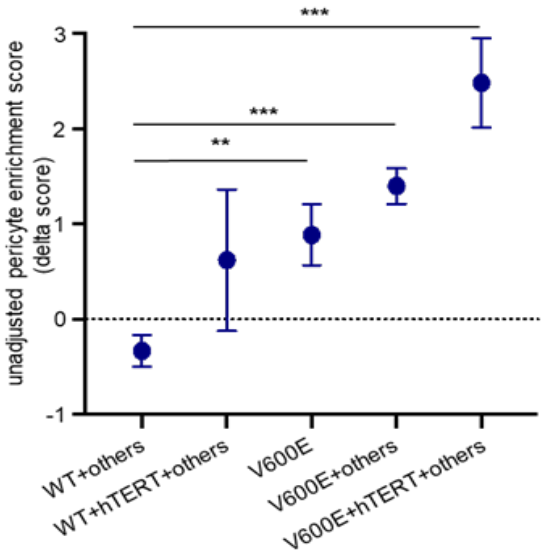
Prete A., et al., and Nucera C., Clinical Cancer Research 2018

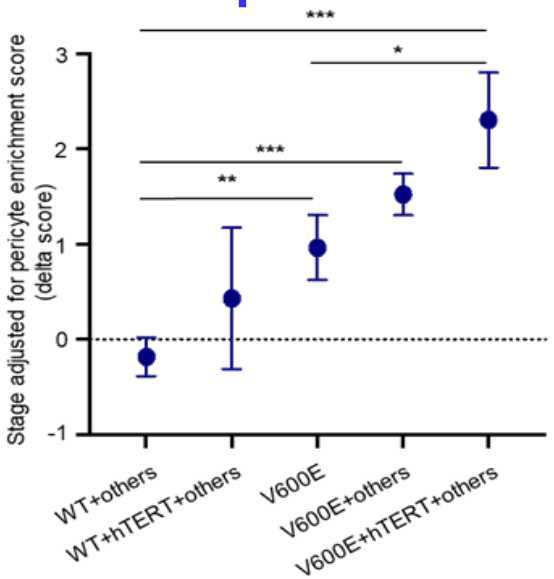
Pericytes abundance score in PTC and normal thyroid (NT) clinical samples

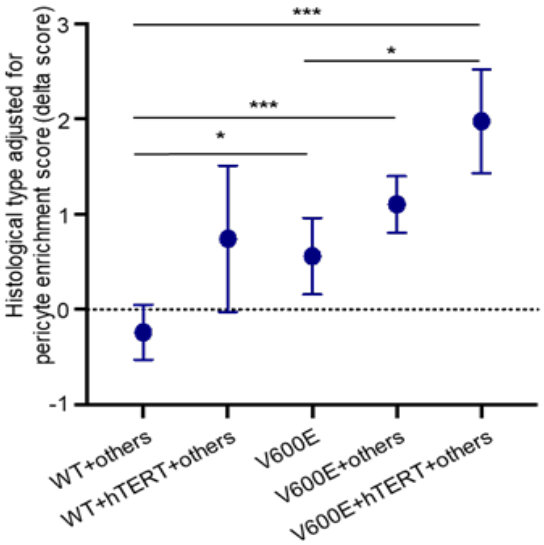


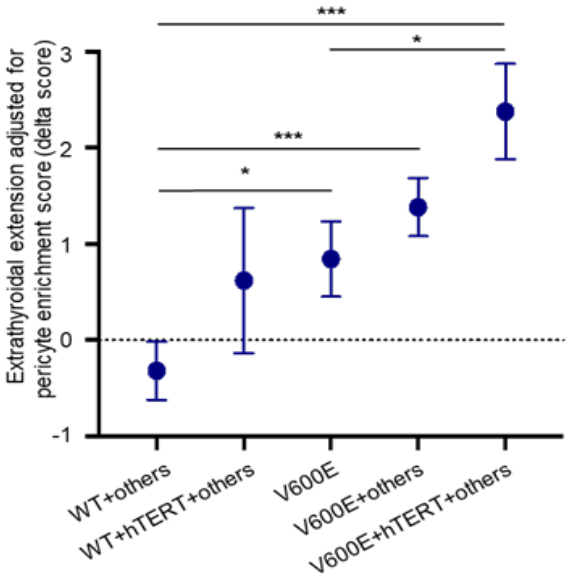
Prete A., et al., and Nucera C., Clinical Cancer Research 2018

Pericyte abundance adjusted to the confounding factors in PTC clinical samples







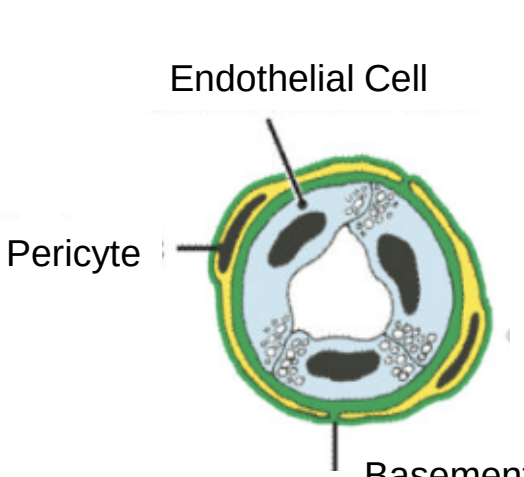


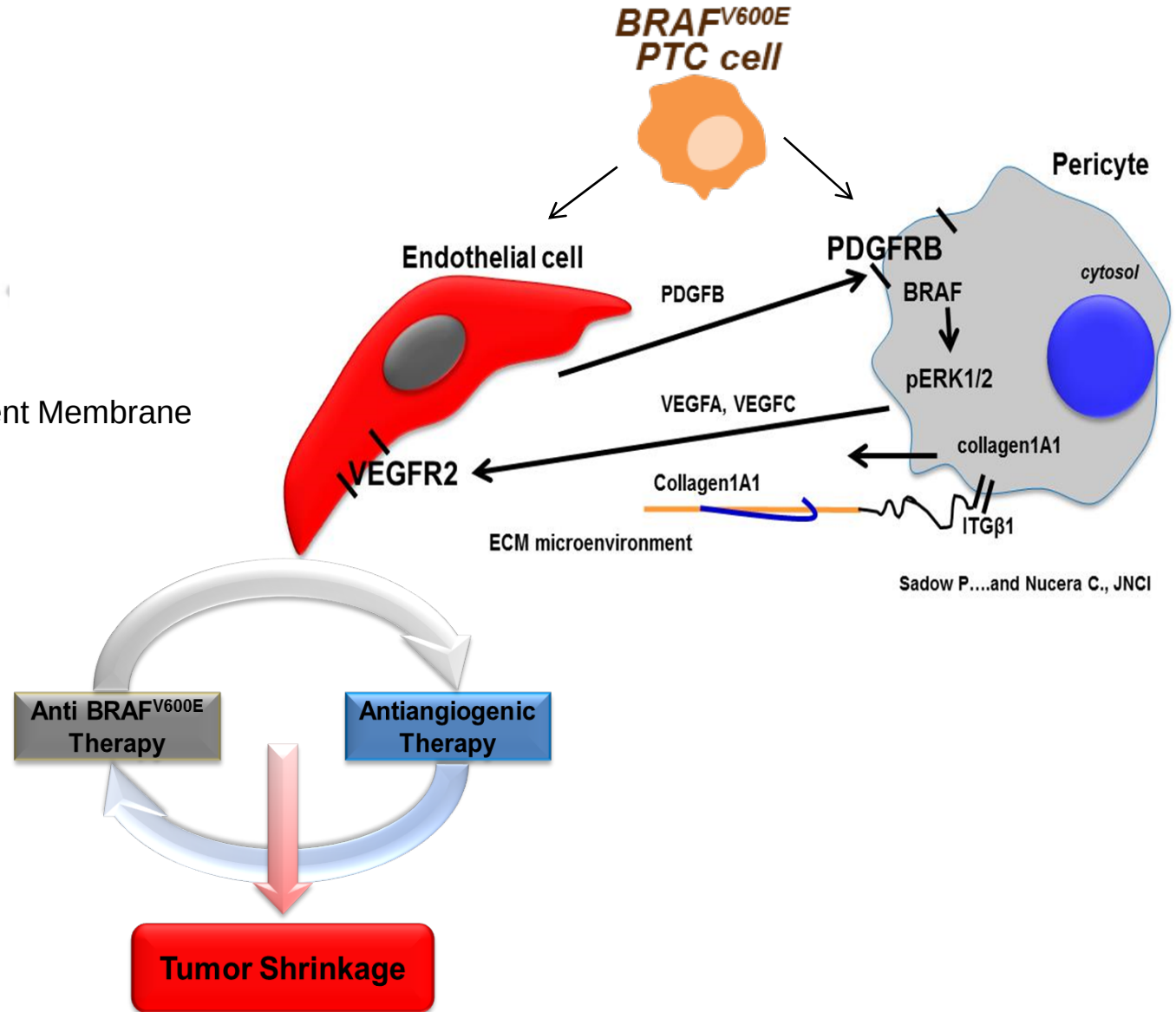
Iesato A., et al., and Nucera C., JCEM 2021

Rationale and Premise

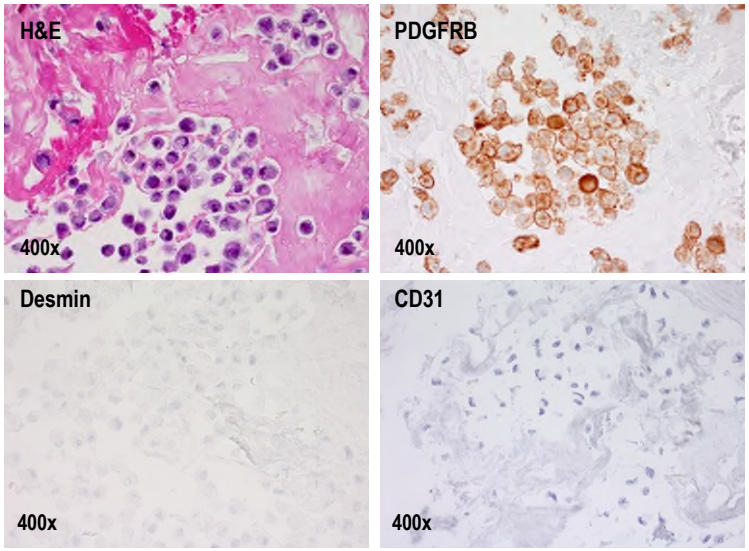
The $BRAF^{V600E}$ oncogene modulates the PTC microenvironment.

Microenvironment pericytes are critical regulators of Tyrosine Kinase (TK)-dependent angiogenic signaling pathways.





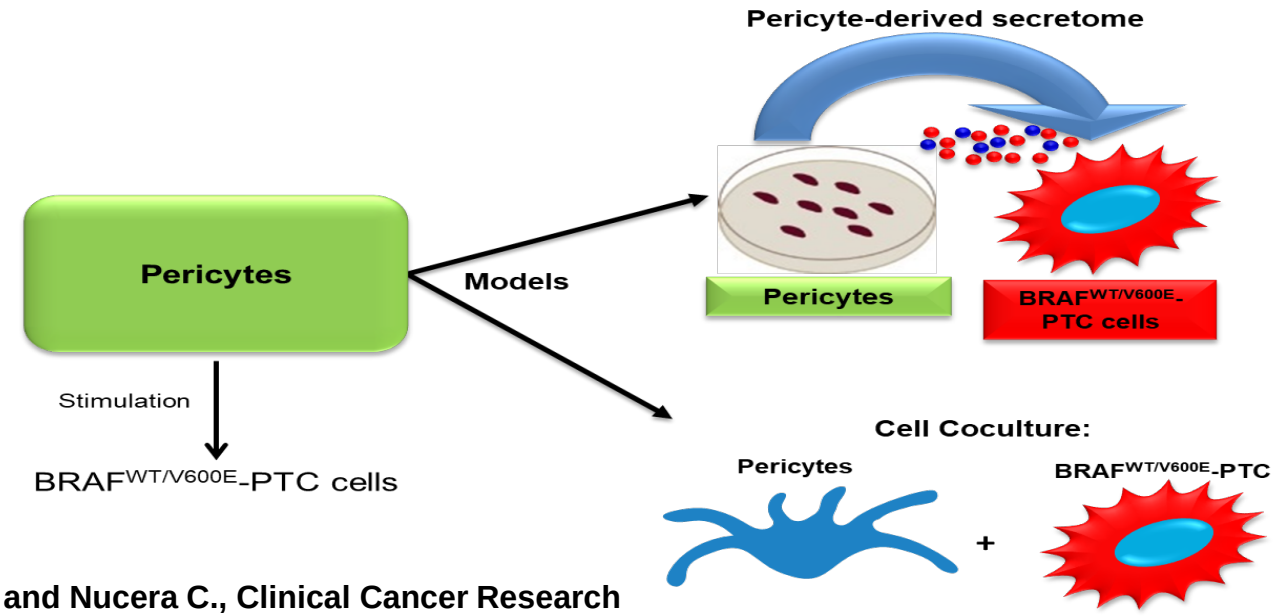
Assessment of perycite markers



Markers	Positive/ Negative	Significance
PDGFRB	Positive	*Pericyte marker*
Desmin	Negative	*Fibroblast marker*
CD31	Negative	*Endothelial marker*

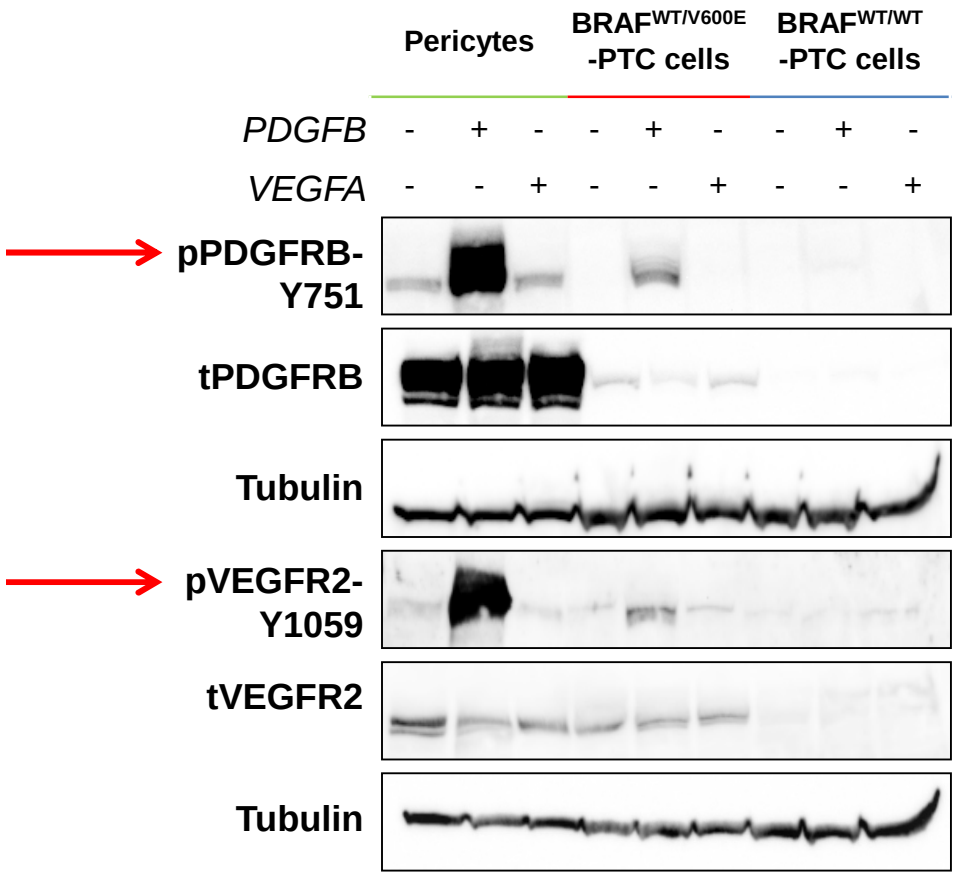
Experimental Design

Workflow to assess the synergy between pericytes and BRAF$^{WT/V600E}$-PTC cells



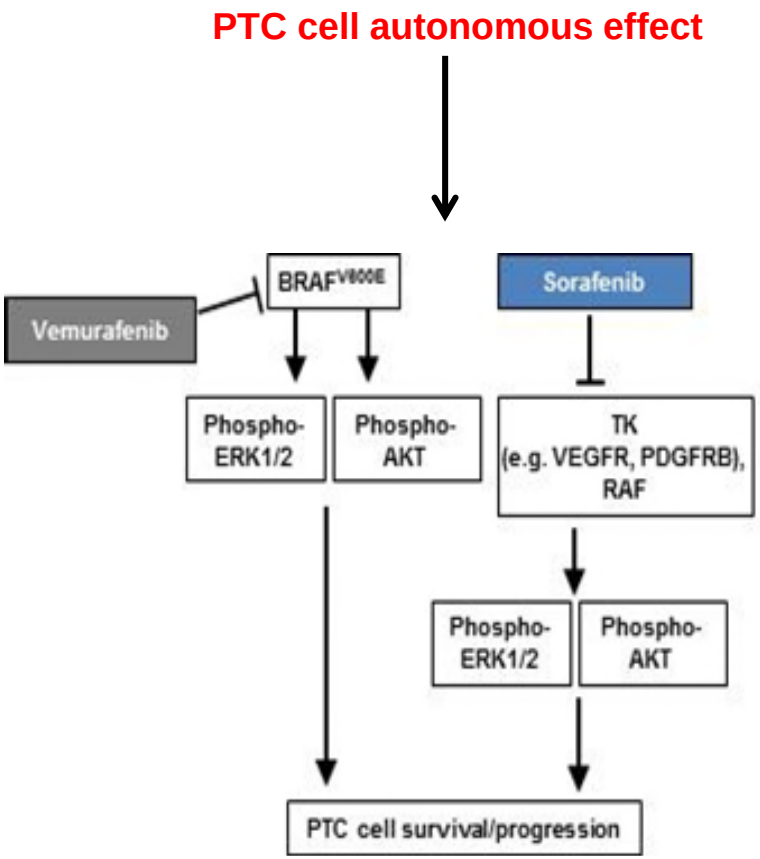
Prete A., et al., and Nucera C., Clinical Cancer Research

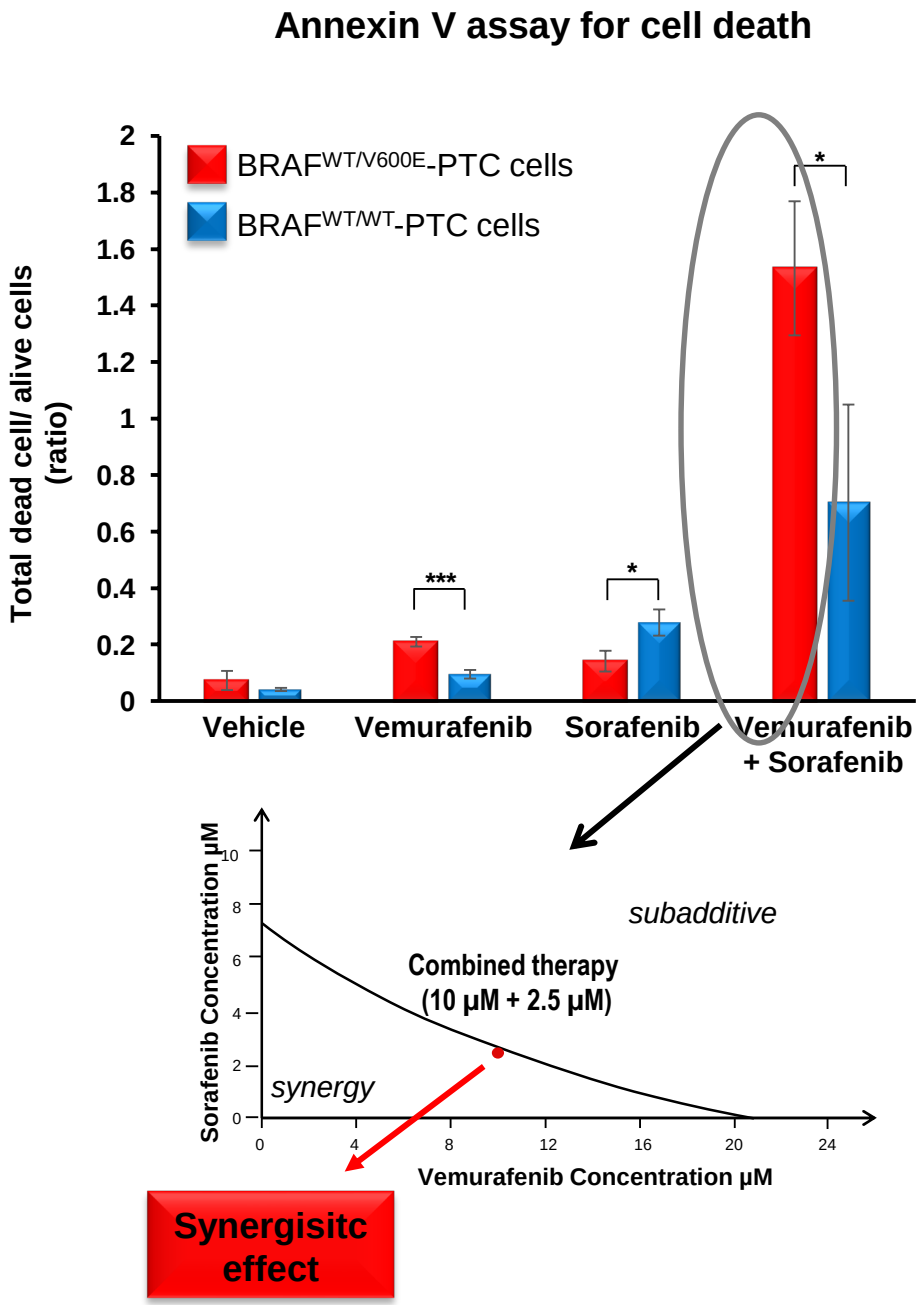
Tyrosine kinases (e.g. VEGFR2 and PDGFRB) are expressed in human pericytes



Prete A., et al., and Nucera C., Clinical Cancer Research

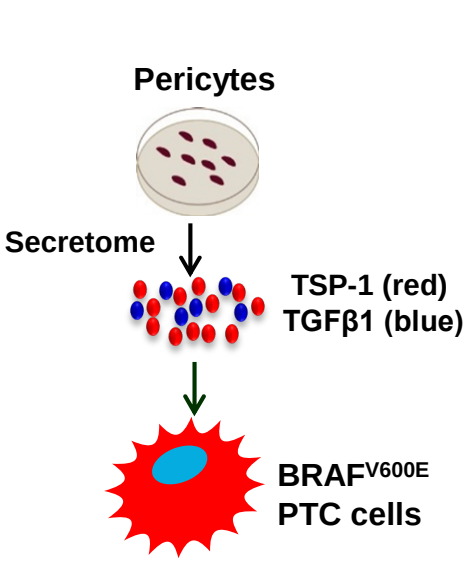
Therapy with $BRAF^{V600E}$ inhibitor plus TKI induces death of PTC cells

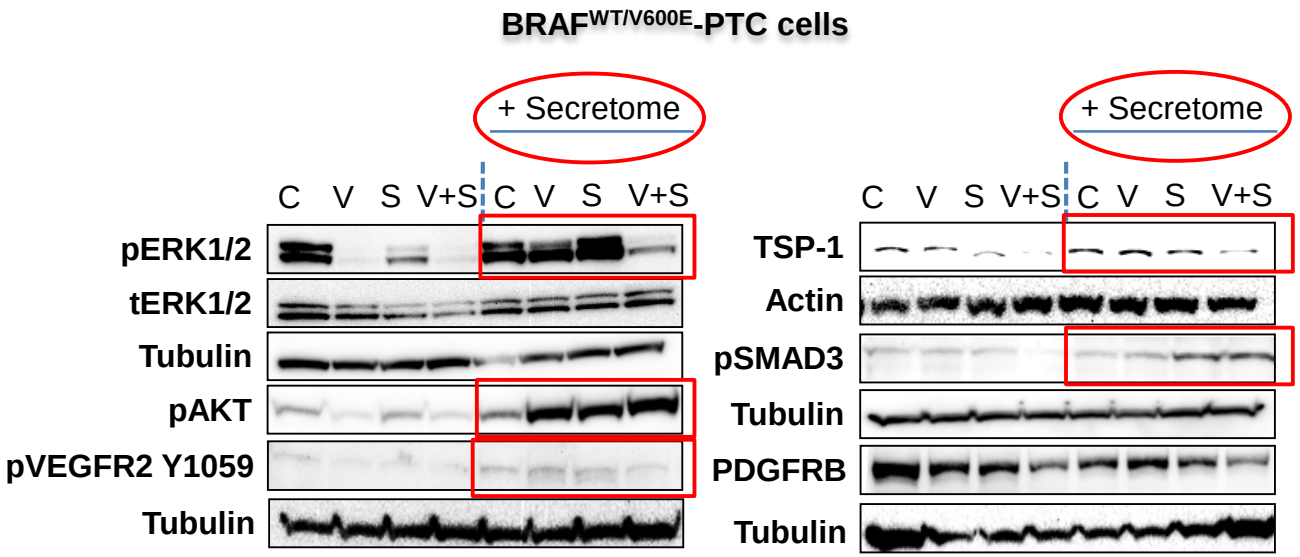




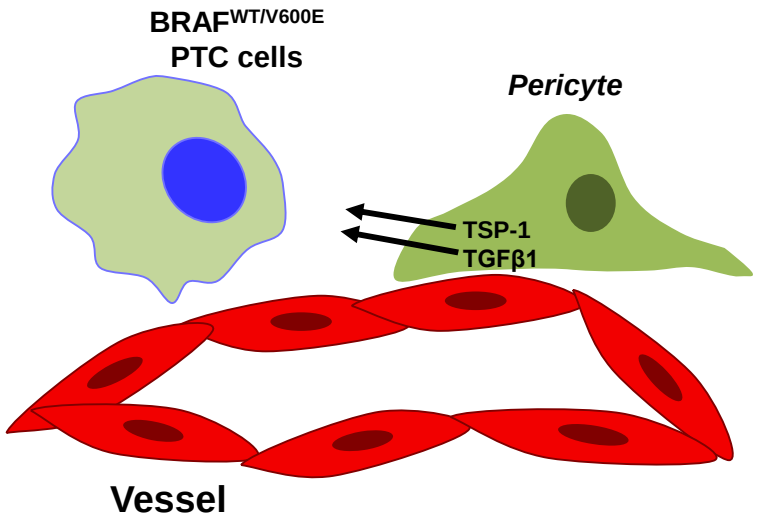
Prete A., et al., and Nucera C., Clinical Cancer Research 2018

Pericyte-derived secretome evocates resistance to targeted therapy in metastatic $BRAF^{WT/V600E}$-PTC cells





C= vehicle
V= vemurafenib
S= sorafenib
V+S= vemurafenib+sorafenib

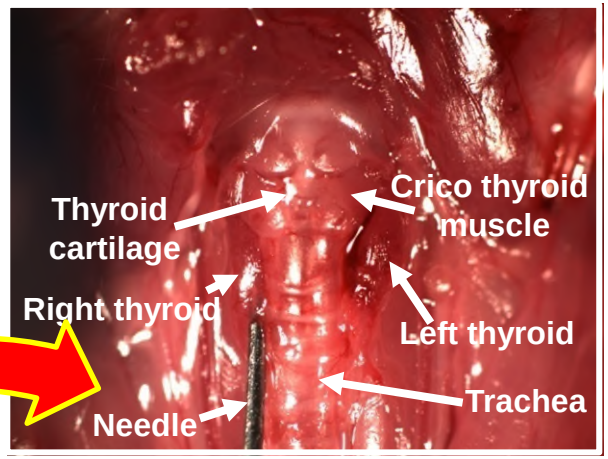


Prete A., et al., and Nucera C., Clinical Cancer Research

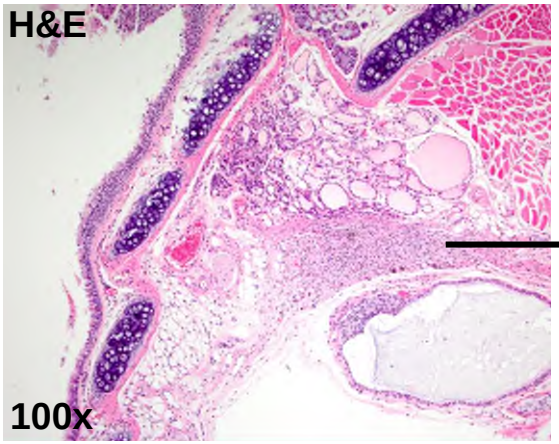
Pre-clinical trial with vemurafenib and sorafenib in a novel orthotopic mouse model of human PTC with heterozygous $BRAF^{WT/V600E}$

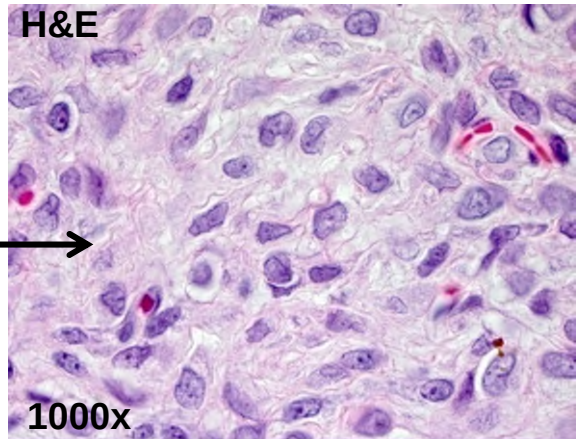
6 weeks post-tumor implantation randomized mice were treated with either vemurafenib, sorafenib, combined therapy, or vehicle by oral gavage

Orthotopic Injection of $BRAF^{WT/V600E}$ PTC in the thyroid of NSG mice



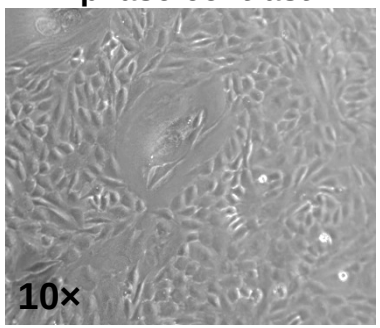
Nucera C. et al. Thyroid 2009



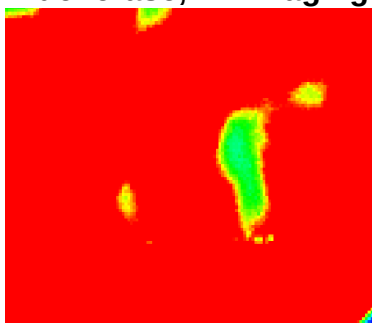


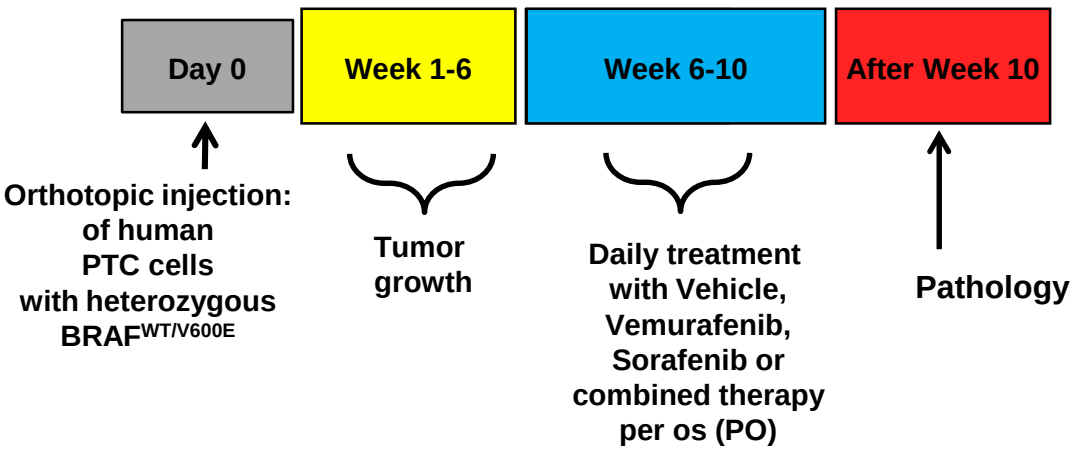
Human invasive PTC cells with $BRAF^{WT/V600E}$

phase-contrast



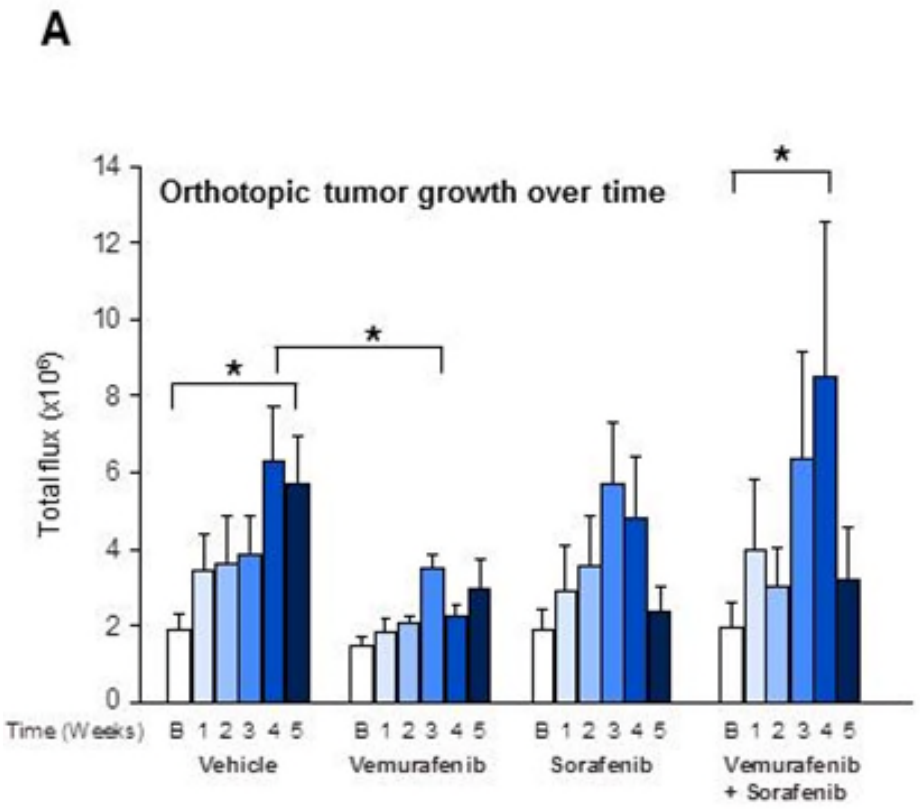
Luciferase, BL imaging

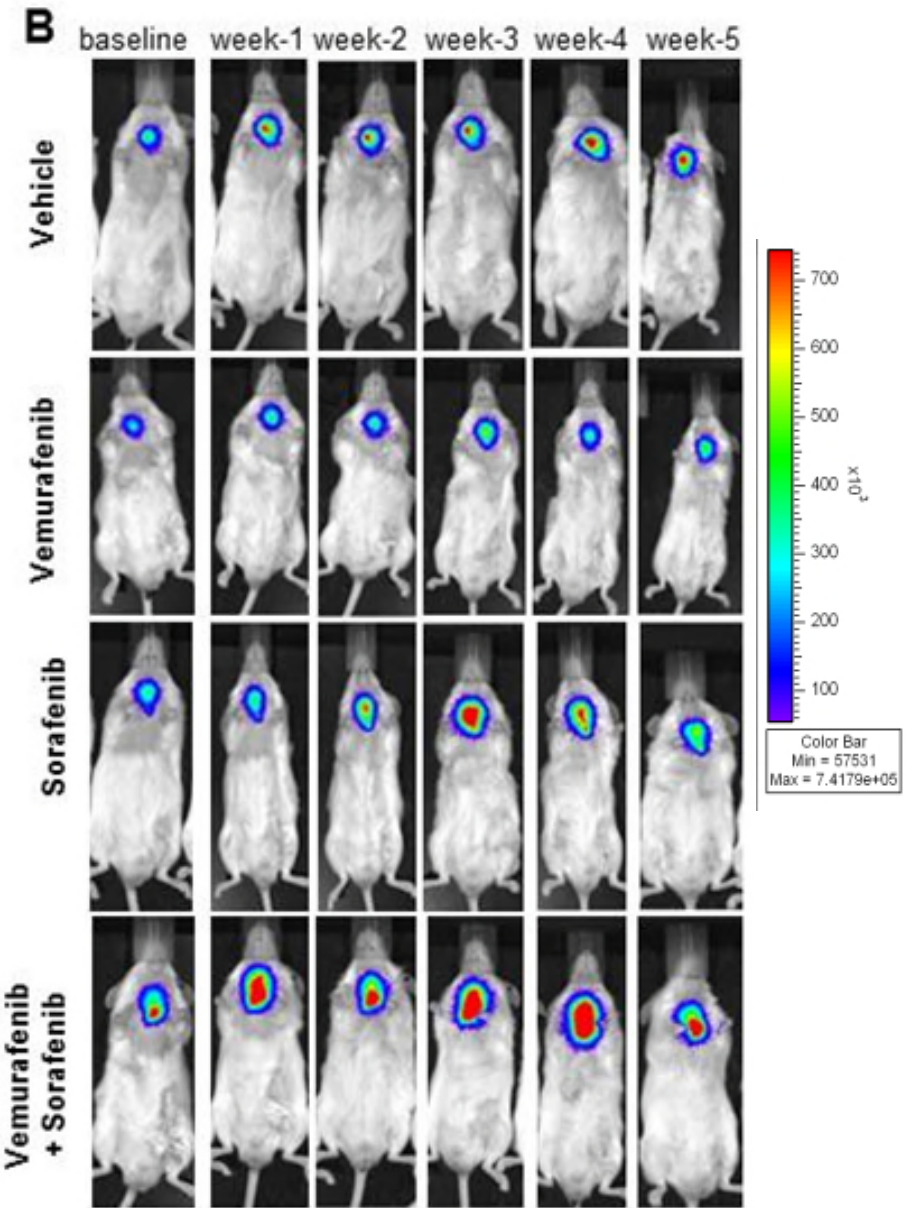




Prete A., et al., and Nucera C., Clinical Cancer Research 2018

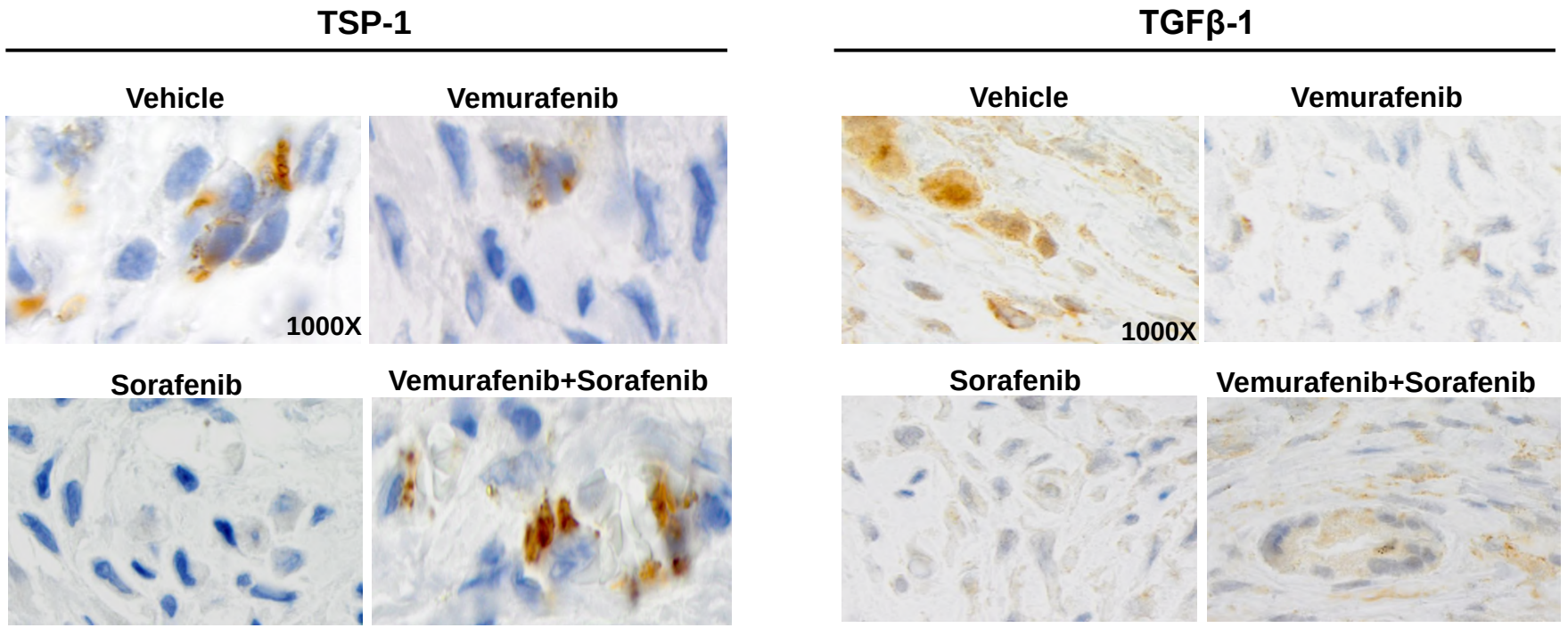
Effects of vemurafenib and sorafenib therapy on orthotopic human $BRAF^{WT/V600E}$-PTC growth





Prete A., et al., and Nucera C., Clinical Cancer Research 2018

Expression of TSP-1 and TGFβ1 in the orthotopic human $BRAF^{WT/V600E}$ PTC



Markers	Vehicle	Vemurafenib	Sorafenib	Vemu.+Sora.
TSP-1	1 TC 2 VE	0 TC 2 VE	0 TC 0 VE	0 TC 2 VE
TGFβ1	2 TC 2 VE	1 TC 2 VE	1 TC 1 VE	1 TC 2 VE

TC= tumor cells
VE= vessel compartment

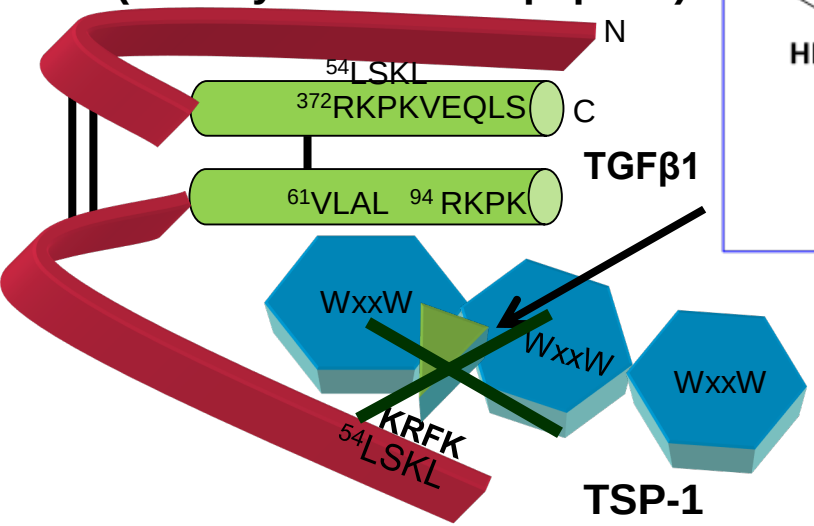
Prete A., et al., and Nucera C., Clinical Cancer Research

Targeting TSP-1 and TGFβ1 interactions

Peptides of key interactions sequences can act as antagonists:
The SRI31277 peptide of the LSKL sequence of LAP prevents TSP-1 binding and activation of latent TGFβ1

Active TGFβ1

LAP (latency-associated peptide)

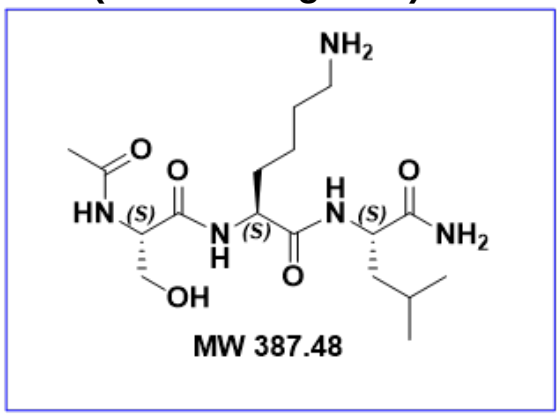


TSP-1
type 1 repeats

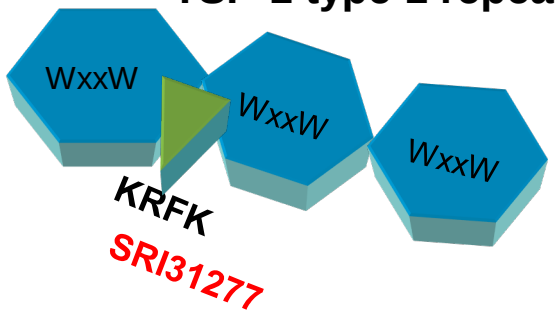
ERK1/2, SMAD3

Tumor Growth

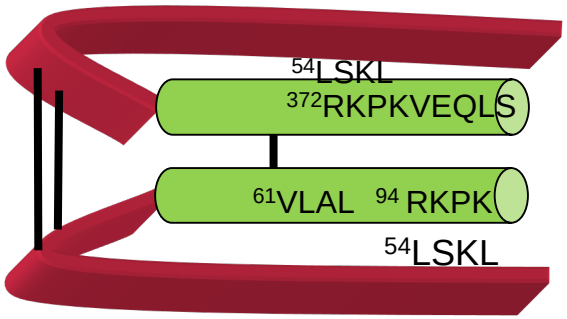
SRI31277
(TSP-1 antagonist)



TSP-1 type 1 repeats



Inactive (Latency) TGFβ1



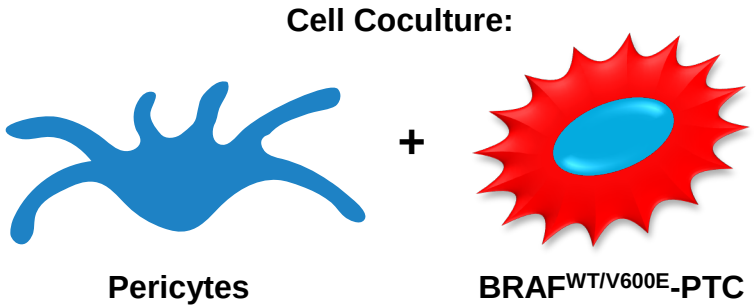
Small latent complex

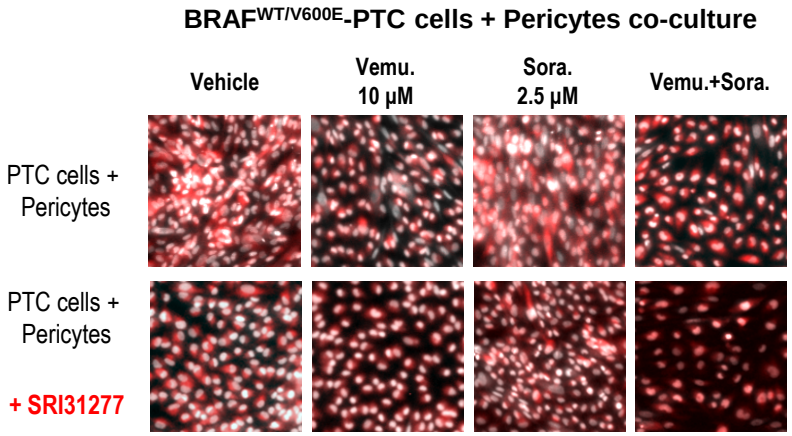
ERK1/2, SMAD3

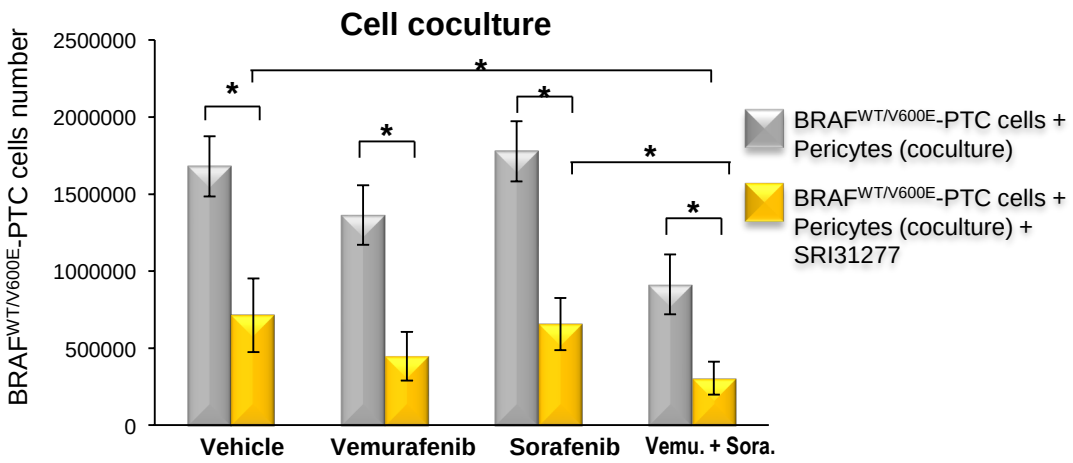
Tumor Growth

Prete A., et al., and Nucera C., Clinical Cancer Research

Targeting TSP-1 inactivates TGFβ1 and reduces growth of $BRAF^{WT/V600E}$ PTC-derived cells cocultured with pericytes

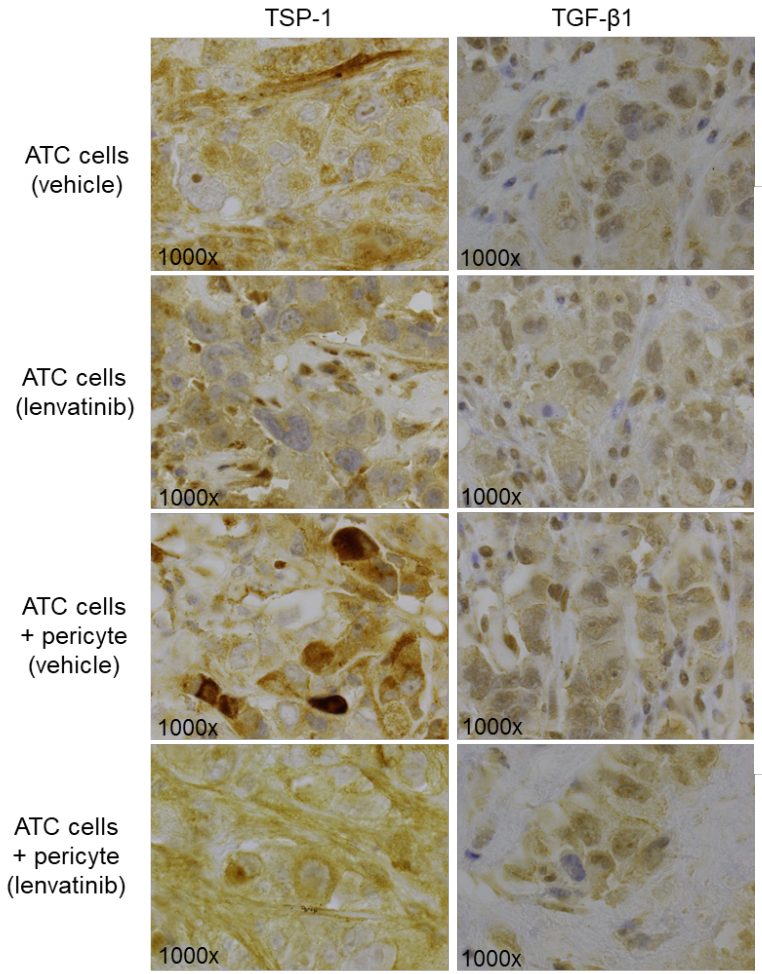






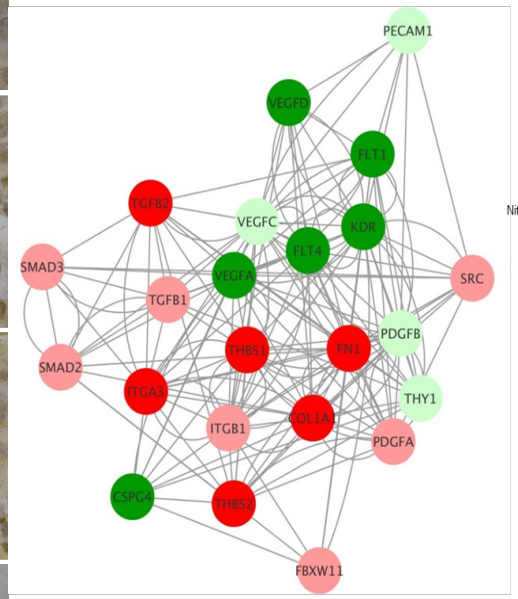
Prete A., et al., and Nucera C., Clinical Cancer Research

TSP-1/TGFβ1 axis elicits gene regulatory networks and pathways important for drug resistance and angio-invasion in BRAF$^{WT/V600E}$ thyroid tumor samples

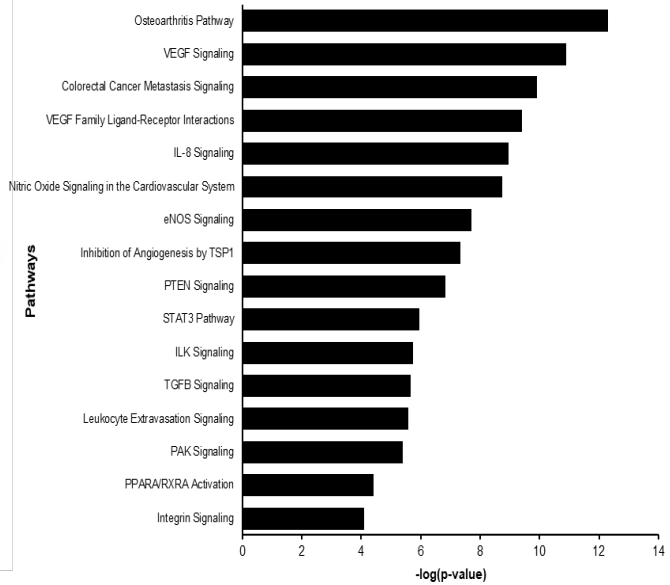


Iesato A., et al., and Nucera C. Thyroid 2023

Gene regulatory intelligence



Mechanistic analysis



Prete A., et al., and Nucera, Clin Cancer Res 2018

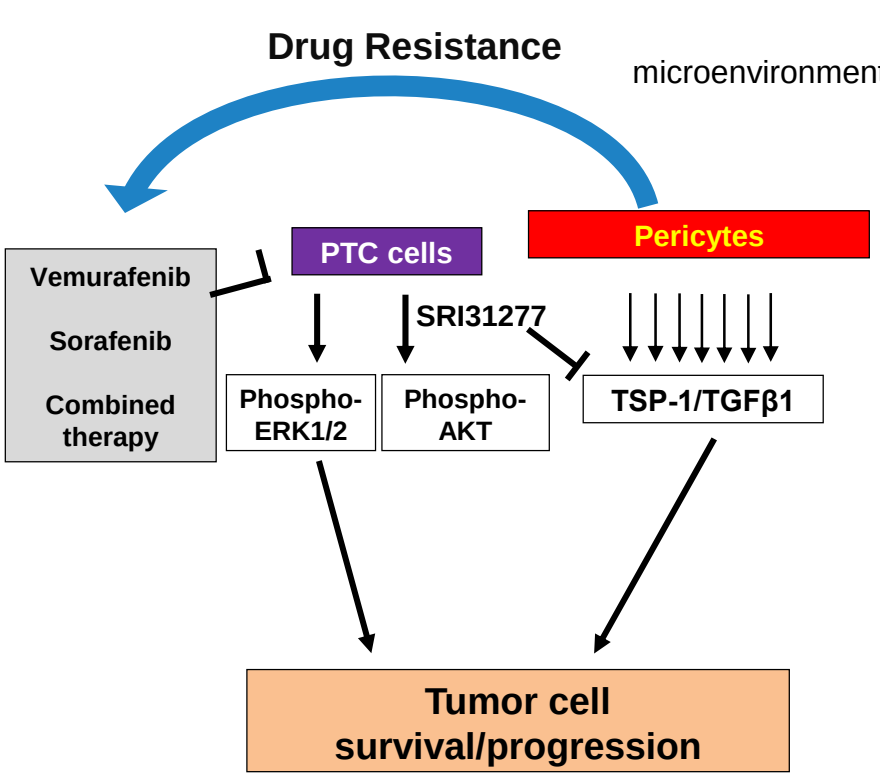
Translational relevance and Impact

Pericytes shield BRAF^{V600E}-PTC cells from targeted therapy via TSP-1/TGFβ1, suggesting this axis as a new therapeutic target for overcoming resistance to BRAF^{V600E} and TK inhibitors.

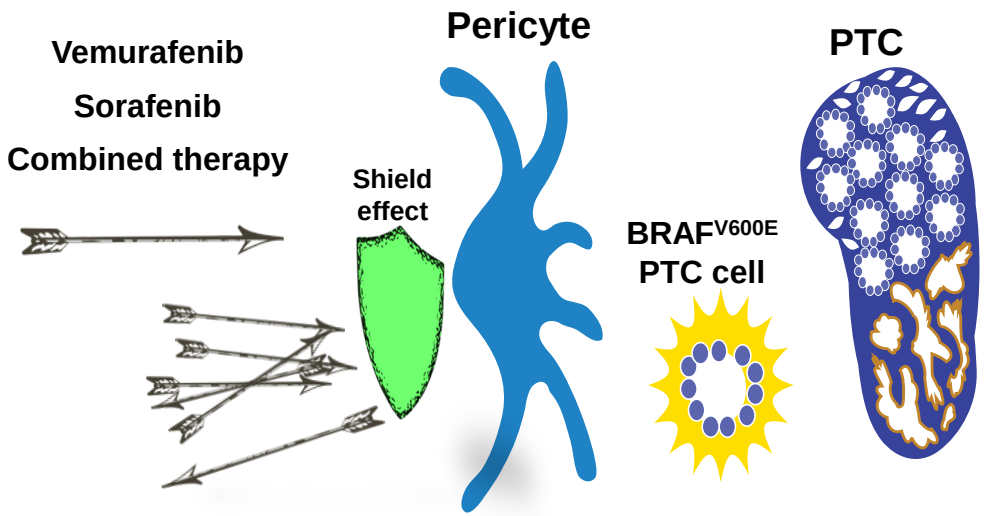
Antagonizing the TSP-1/TGFβ1 axis may represent a novel therapeutic approach with translational applications for BRAF$^{WT/V600E}$-PTC resistant to targeted therapies.

TSP-1 is a potential biomarker for assessing therapeutic response to BRAF^{V600E} and TK inhibitors in patients with invasive BRAF$^{WT/V600E}$-PTC.

New model for resistance to BRAF^{V600E} inhibitors and TKI via pericyte



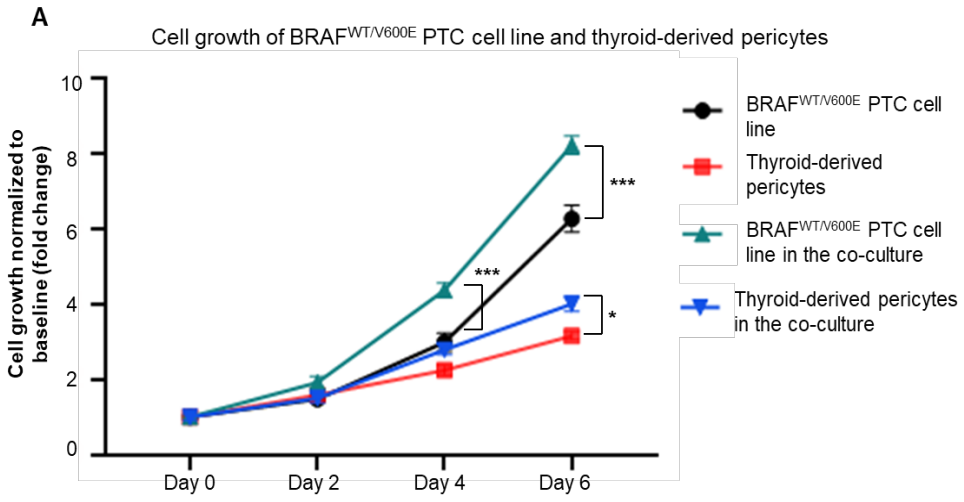
Pericytes shield BRAF$^{WT/V600E}$-PTC cells from targeted terapy

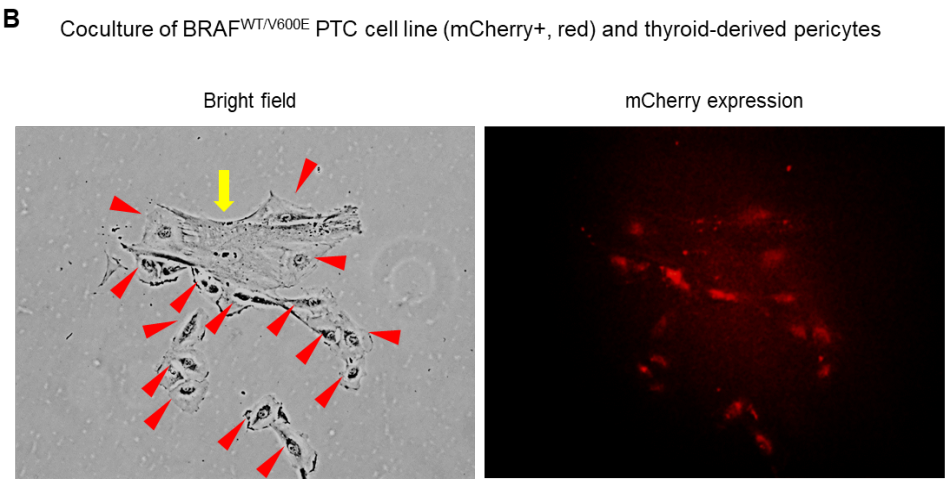


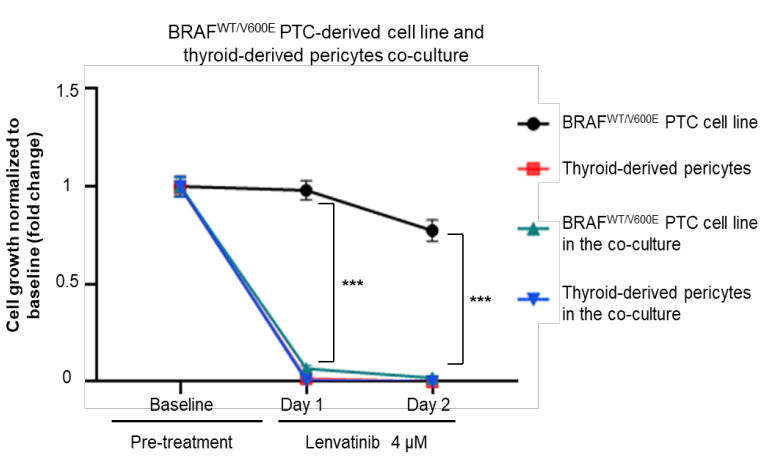
Prete A., et al., and Nucera C., Clinical Cancer Research

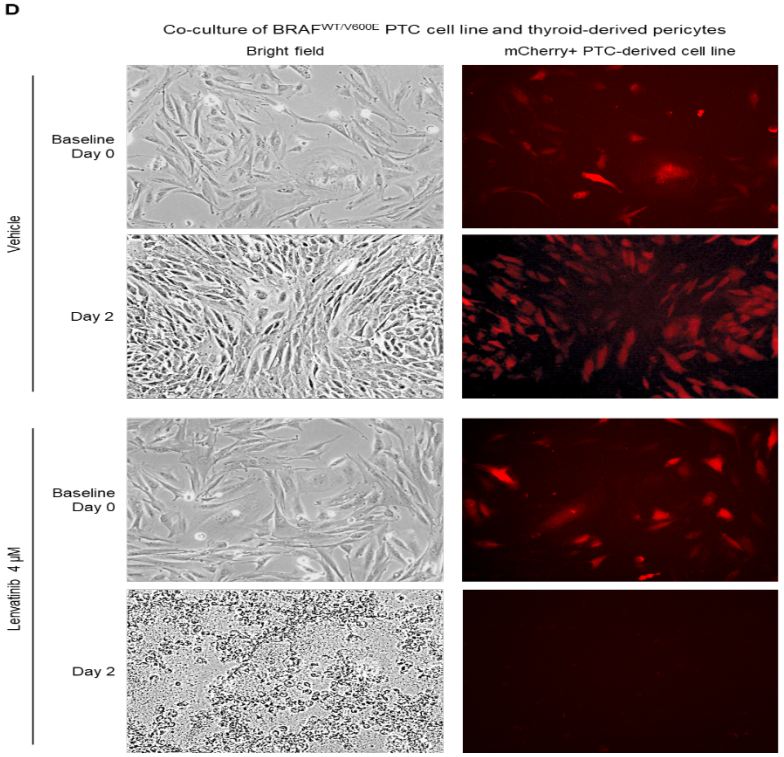
Thyroid-derived pericytes co-cultured with BRAF$^{WT/V600E}$ PTC-derived cells promote tumor cell growth

Lenvatinib elicits significant and robust inhibitory effects on *BRAF$^{WT/V600E}$*-PTC cell growth by targeting pericytes



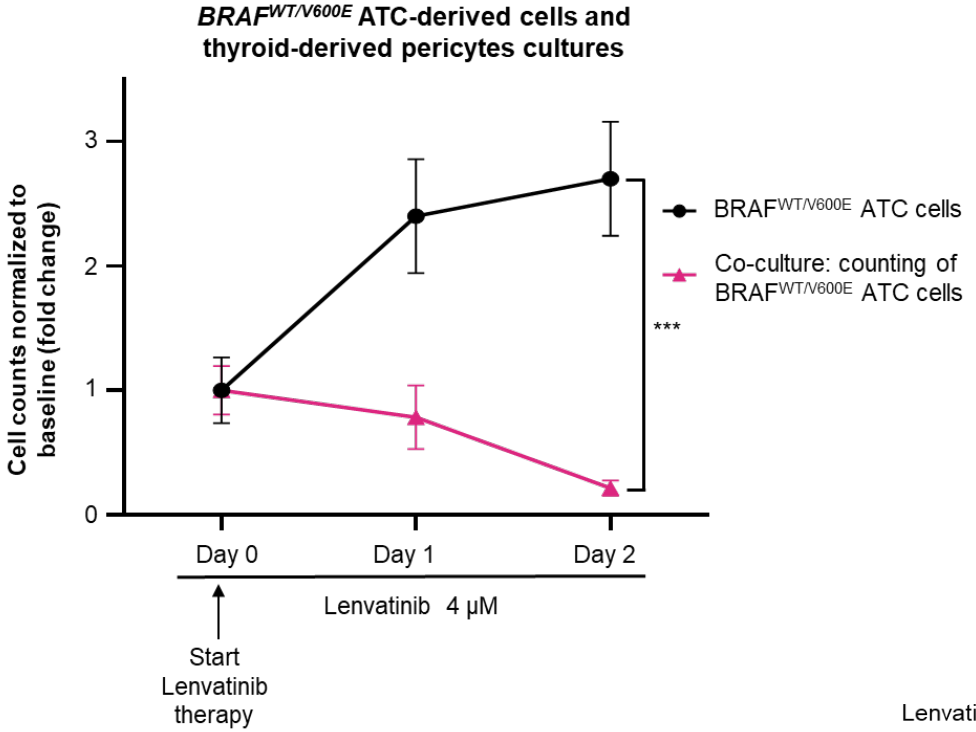


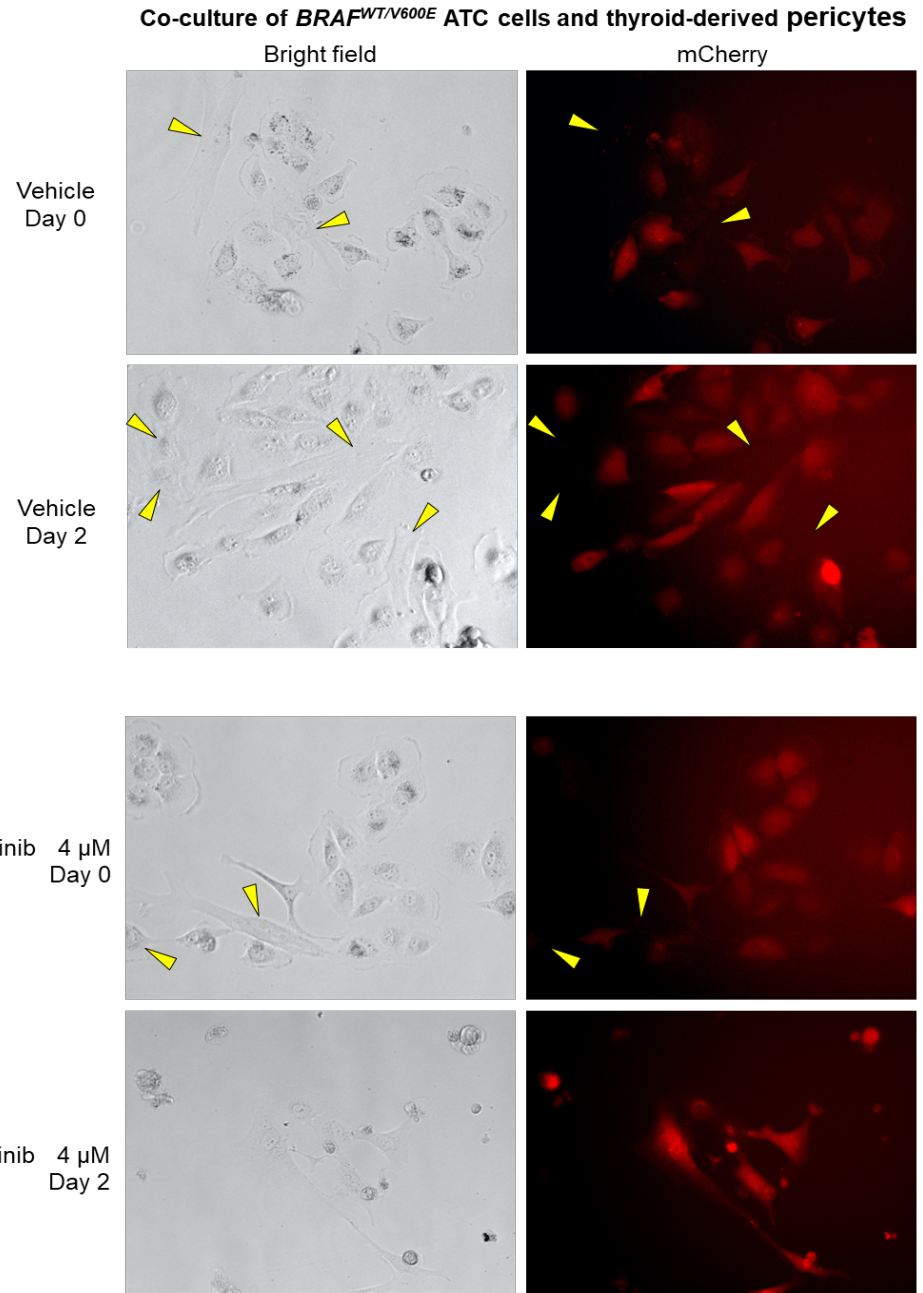




Iesato A., et al., and Nucera C., JCEM 2021

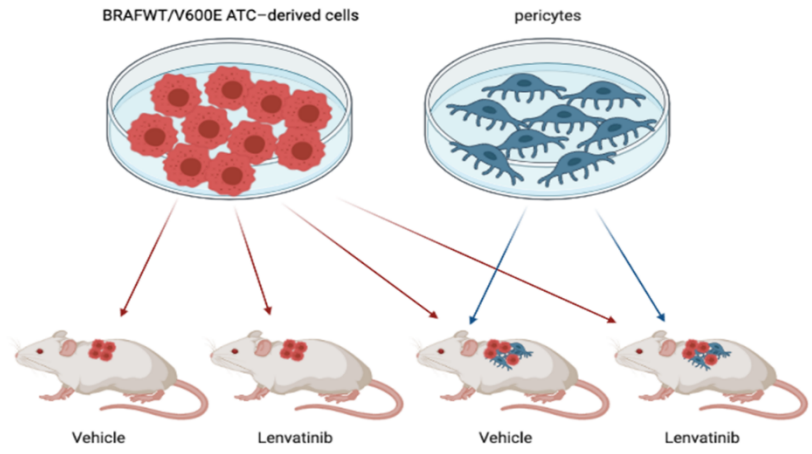
The inhibitory effects by lenvatinib on *BRAF*$^{WT/V600E}$-ATC cells significantly occurred when tumor cells were co-cultured with thyroid-derived pericytes

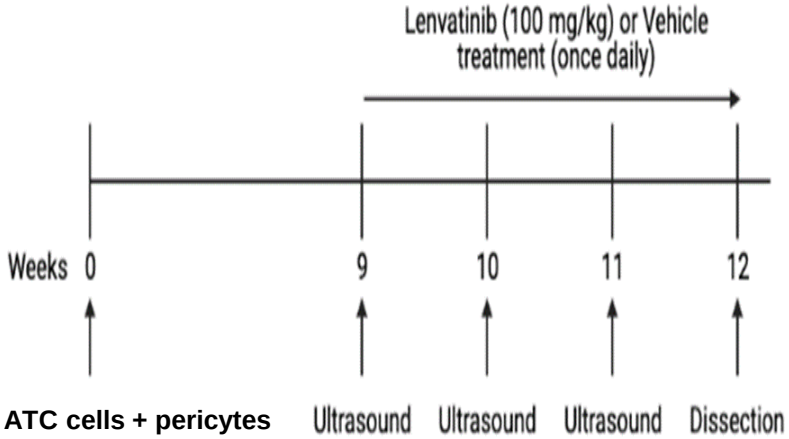




Iesato A., et al., and Nucera C. Thyroid 2023

$BRAF^{WT/V600E}$-ATC cells co-cultured with pericytes showed significant therapeutic response to lenvatinib *in vivo*





B-mode images

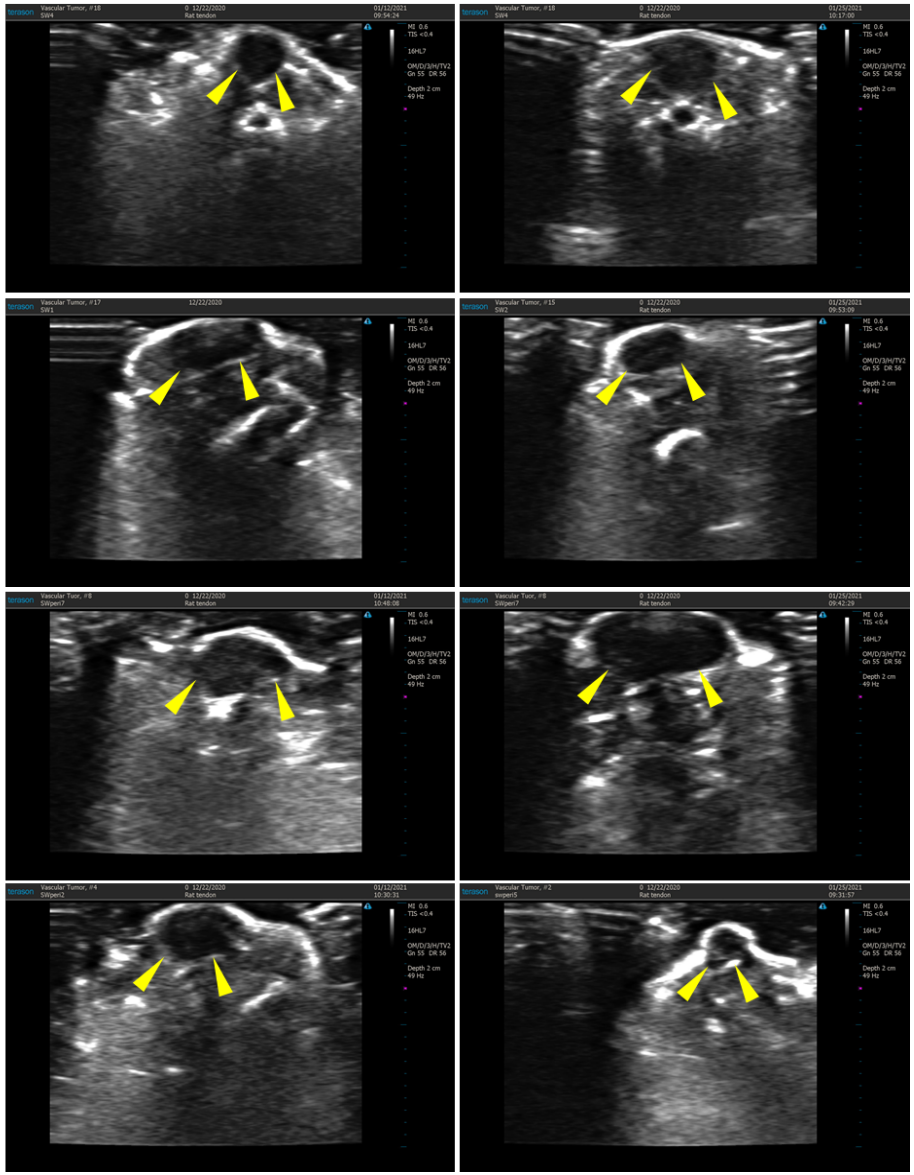
First week of treatment | Week 3 (treatment)

ATC cells Vehicle

ATC cells Lenvatinib

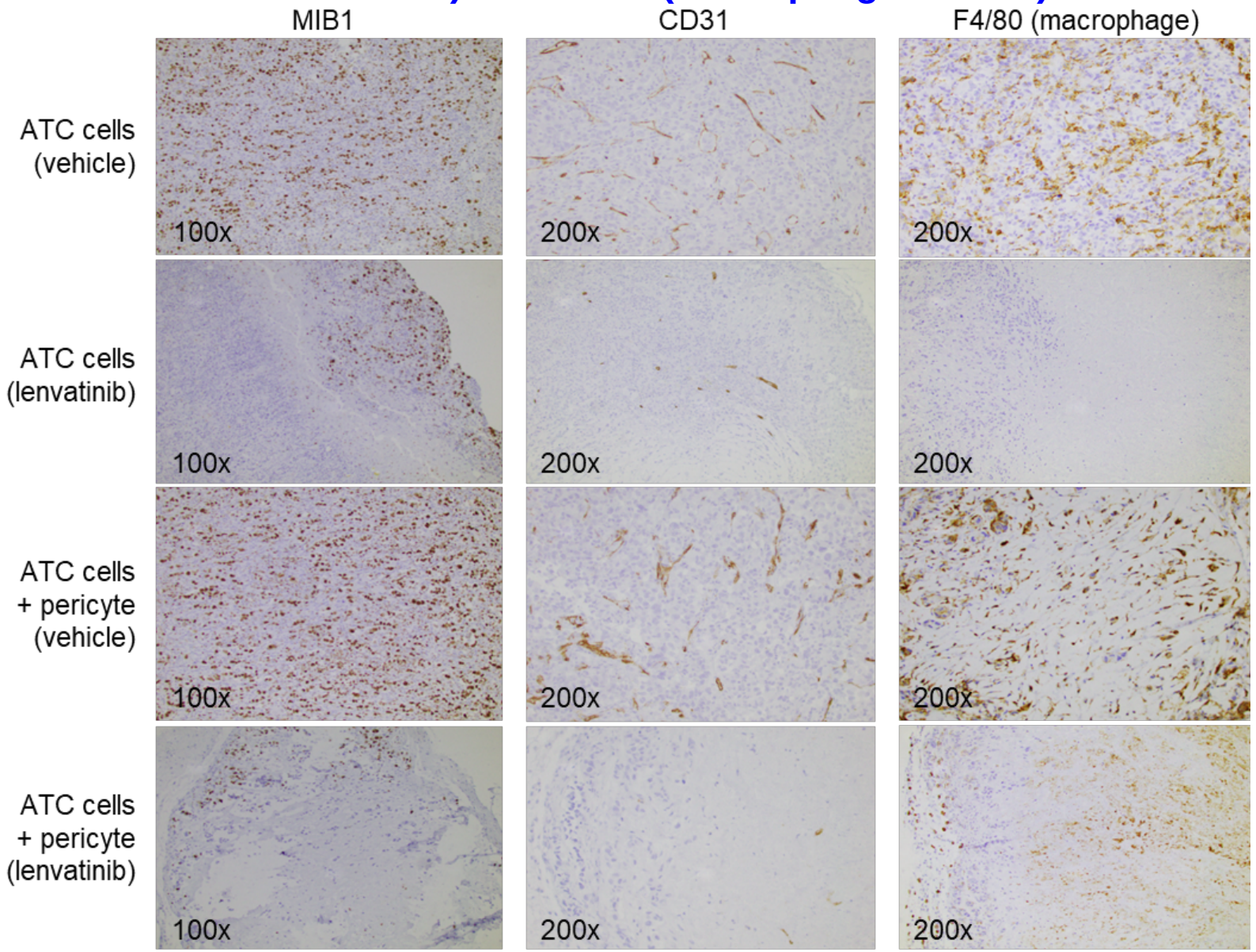
ATC cells +pericyte Vehicle

ATC cells +pericyte Lenvatinib



Iesato A., et al., and Nucera C. Thyroid 2023

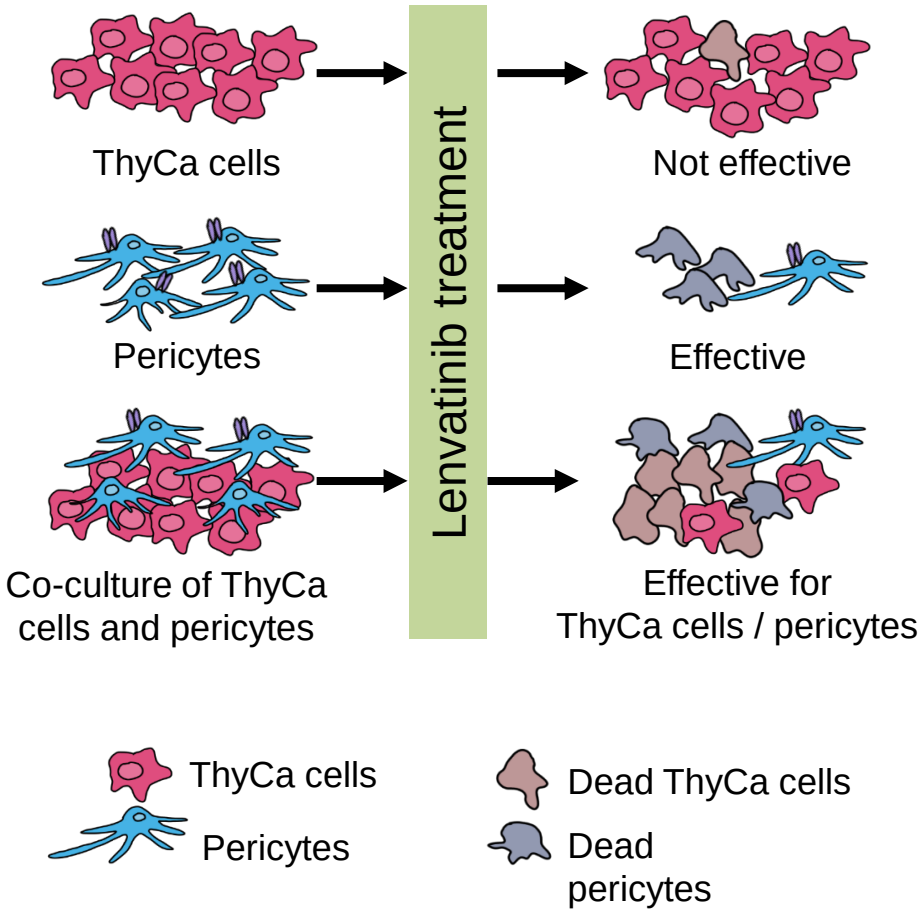
Lenvatinib treatment substantially decreased the number of both tumor cells and pericytes, as well as MIB1 (cell proliferation marker), CD31 (blood endothelial cells marker) and F4-80 (macrophage marker)

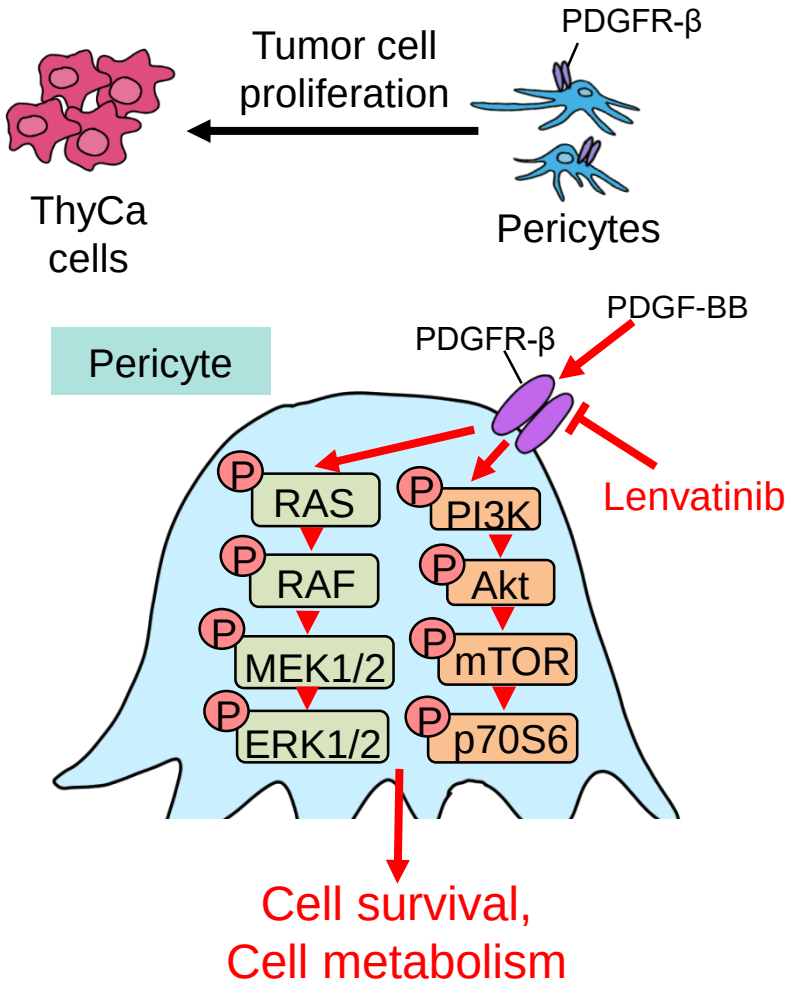


Iesato A., et al., and Nucera C. Thyroid 2023

Translational Implications

Degree of pericyte abundance may be an attractive prognostic marker in assessing pharmacotherapeutic options

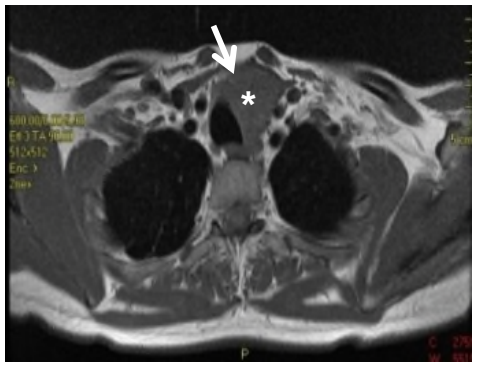


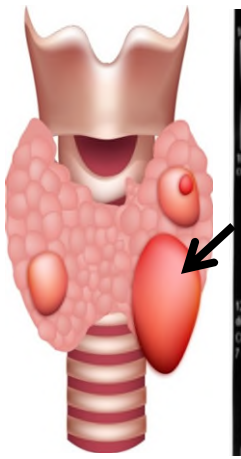


Iesato A., et al., and Nucera C., JCEM 2021
Iesato A., et al and Nucera C., Thyroid 2023

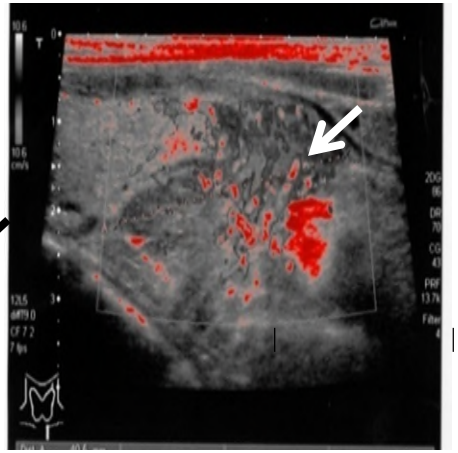
Thyroid tumors derived from pericyte with stem cell-like functions harbor $BRAF^{V600E}$ mutation

MRI

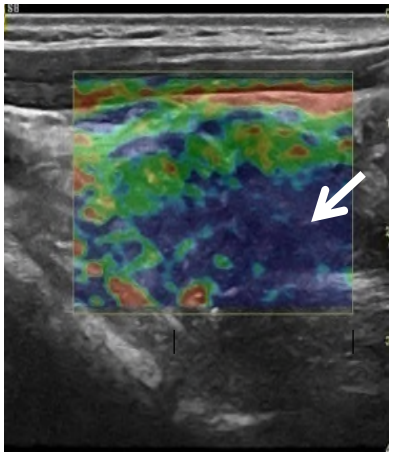




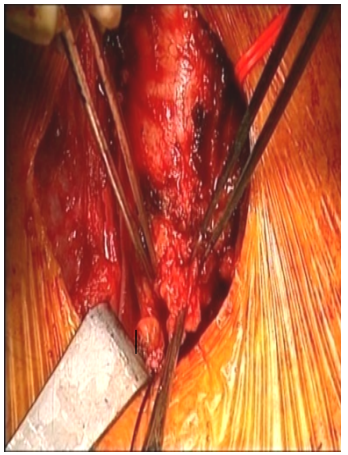
Doppler



Elastography

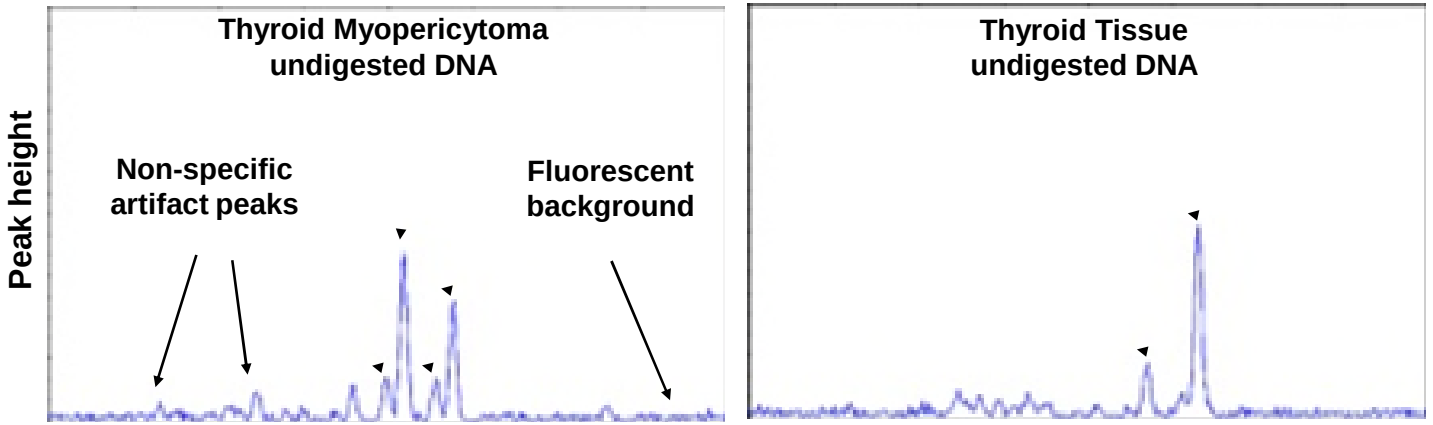


Surgery



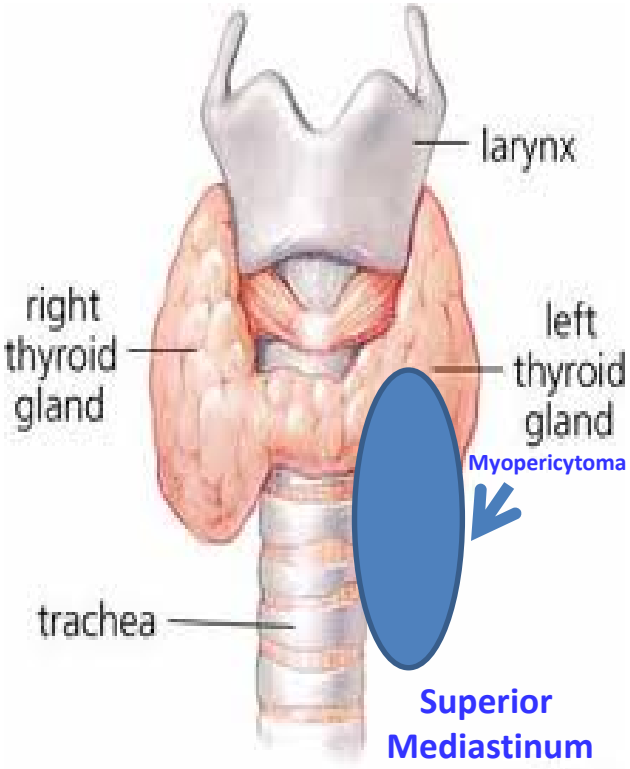
Clonality assay (X-chromosome inactivation assay)

Methylation profile

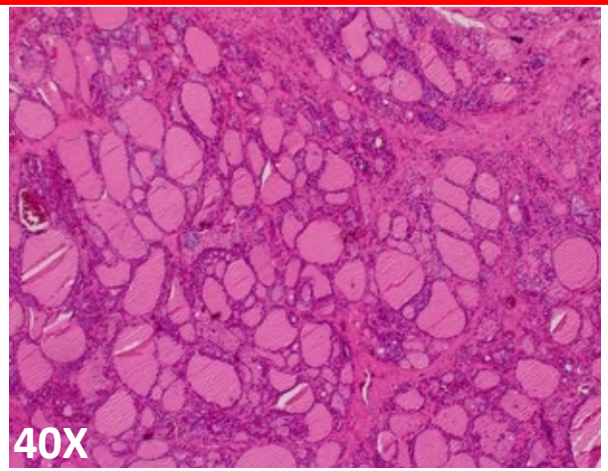


Sadow P….and Nucera C., JNCI 2014

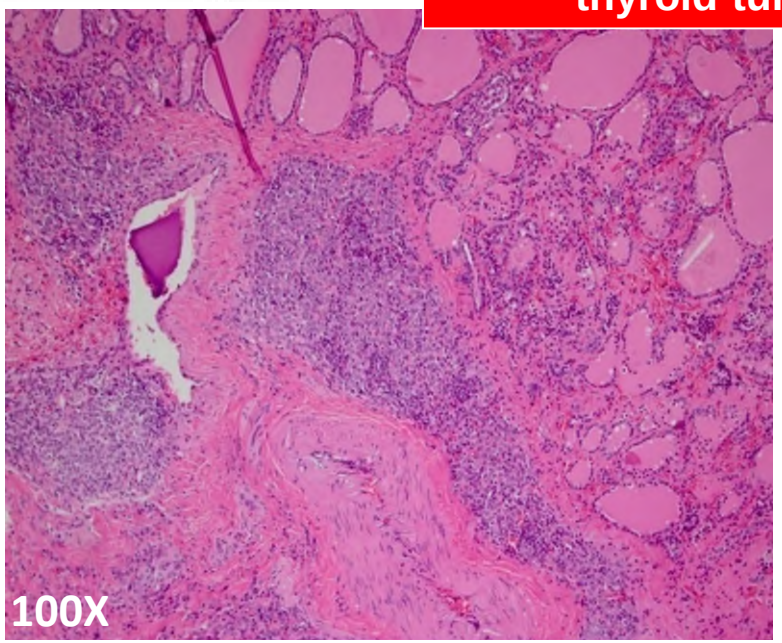
Pericyte-derived tumors

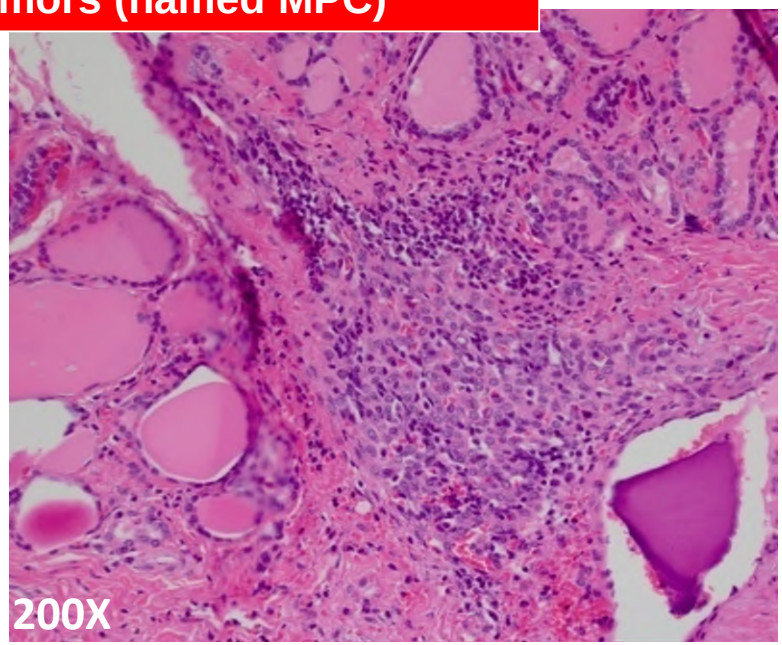


Benign/Normal Thyroid



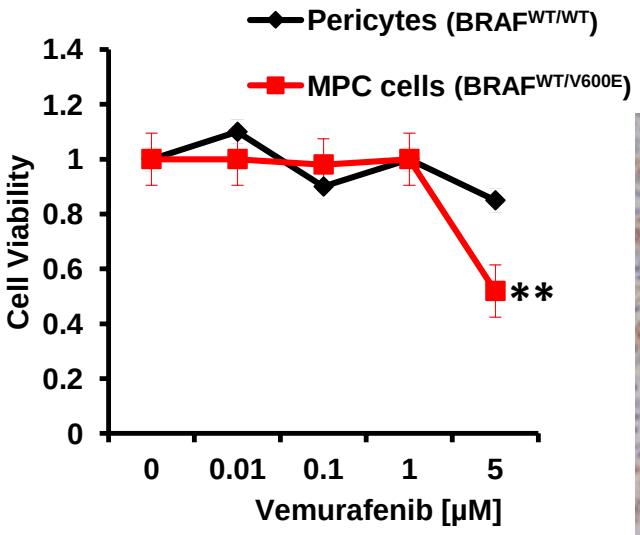
$BRAF^{V600E}$ positive pericyte-derived thyroid tumors (named MPC)

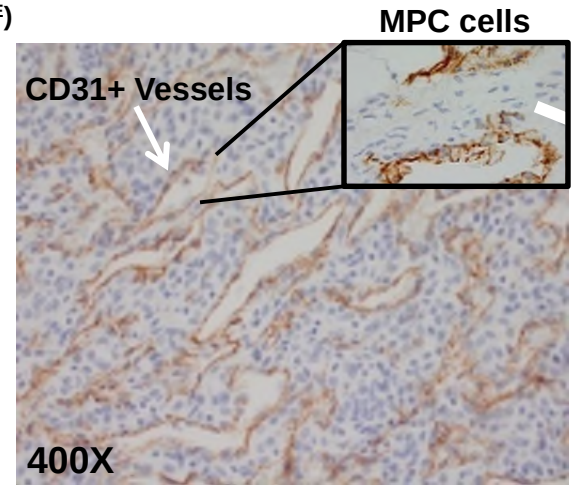


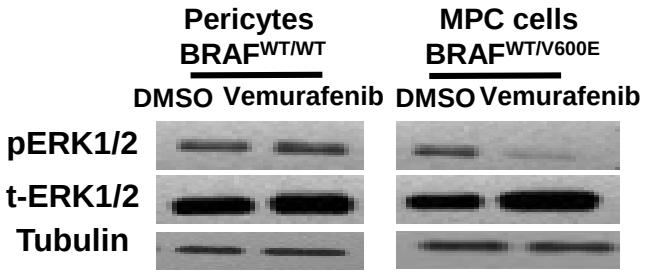


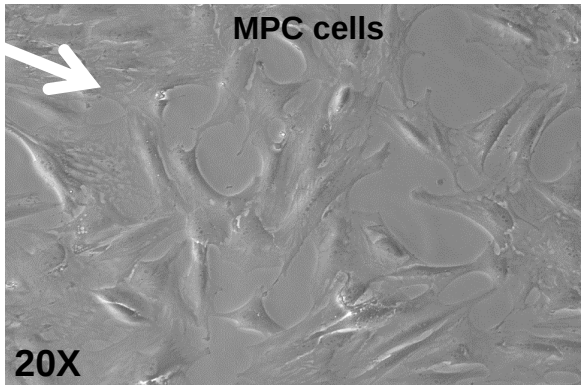
Results

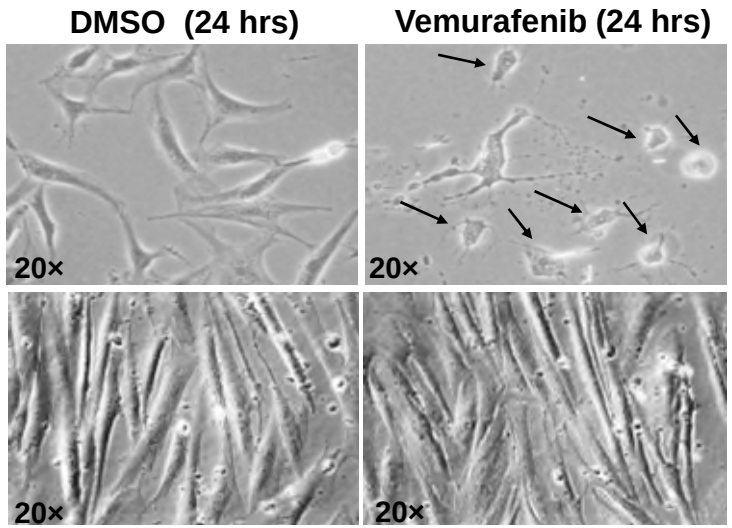
Targeting $BRAF^{V600E}$ by vemurafenib decreases viability of $BRAF^{V600E}$ positive human thyroid myopericytoma (MPC) cells with stem cell-like features

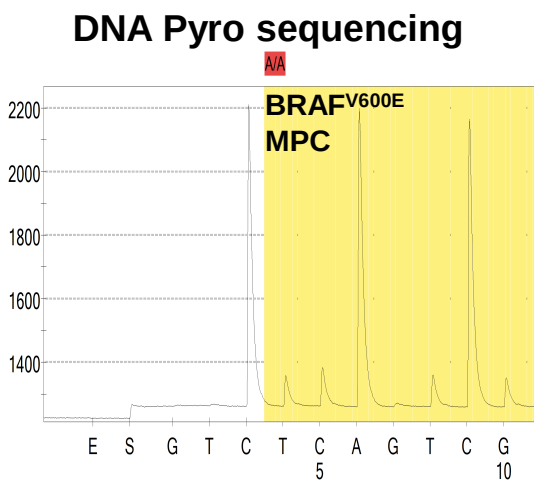


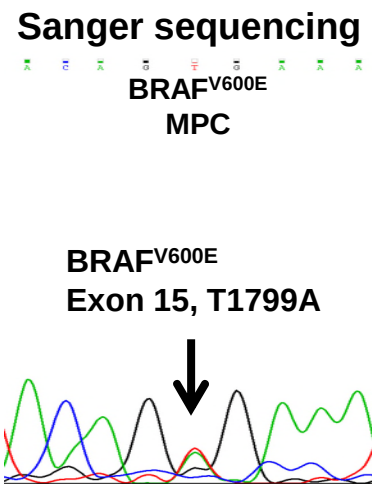








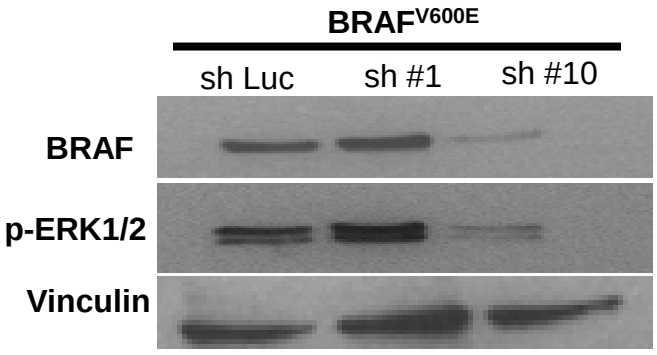


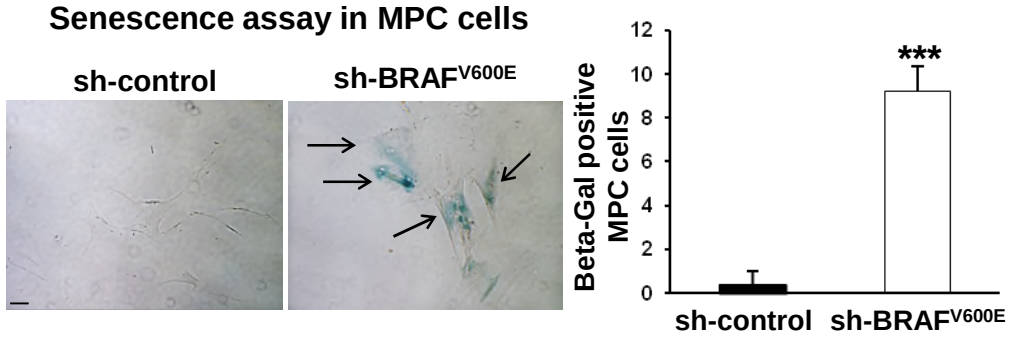


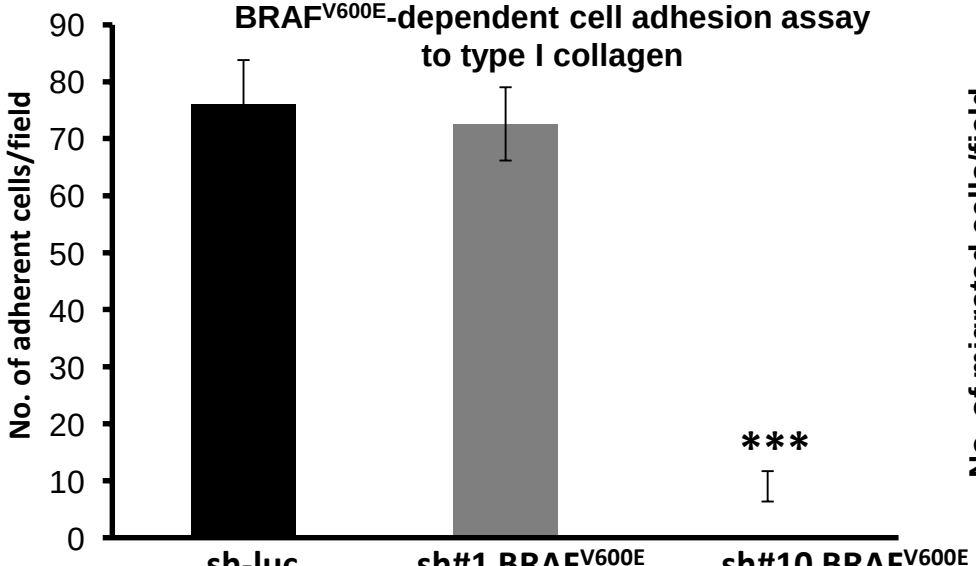
Sadow P….and Nucera C., JNCI 2014

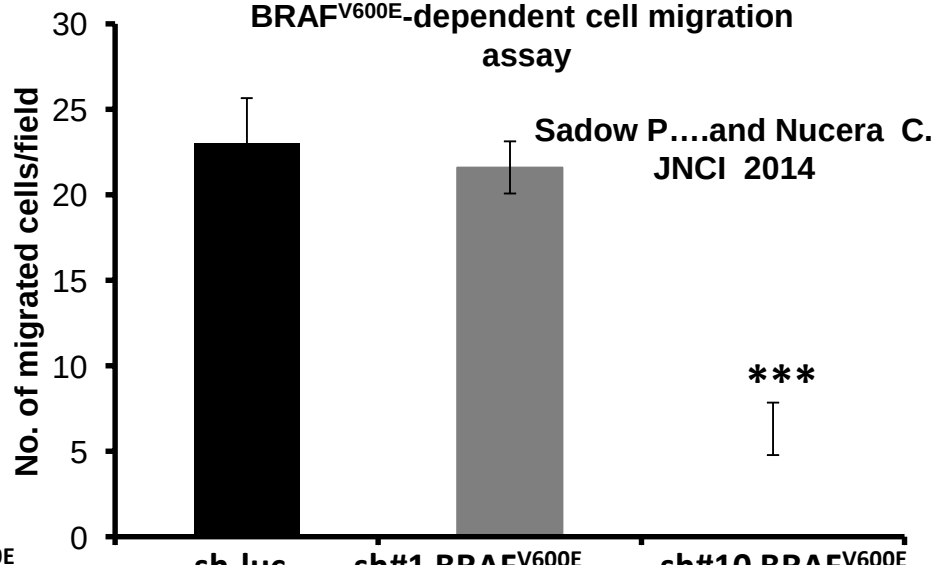
Results

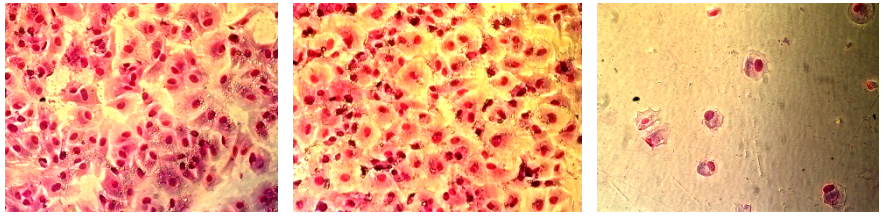
Knockdown of BRAF^{V600E} induce cell senescence and prevents collagen-mediated cell adhesion and migration in primary MPC cells with BRAF^{V600E}

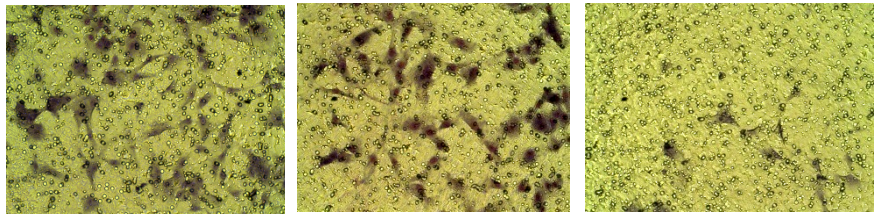




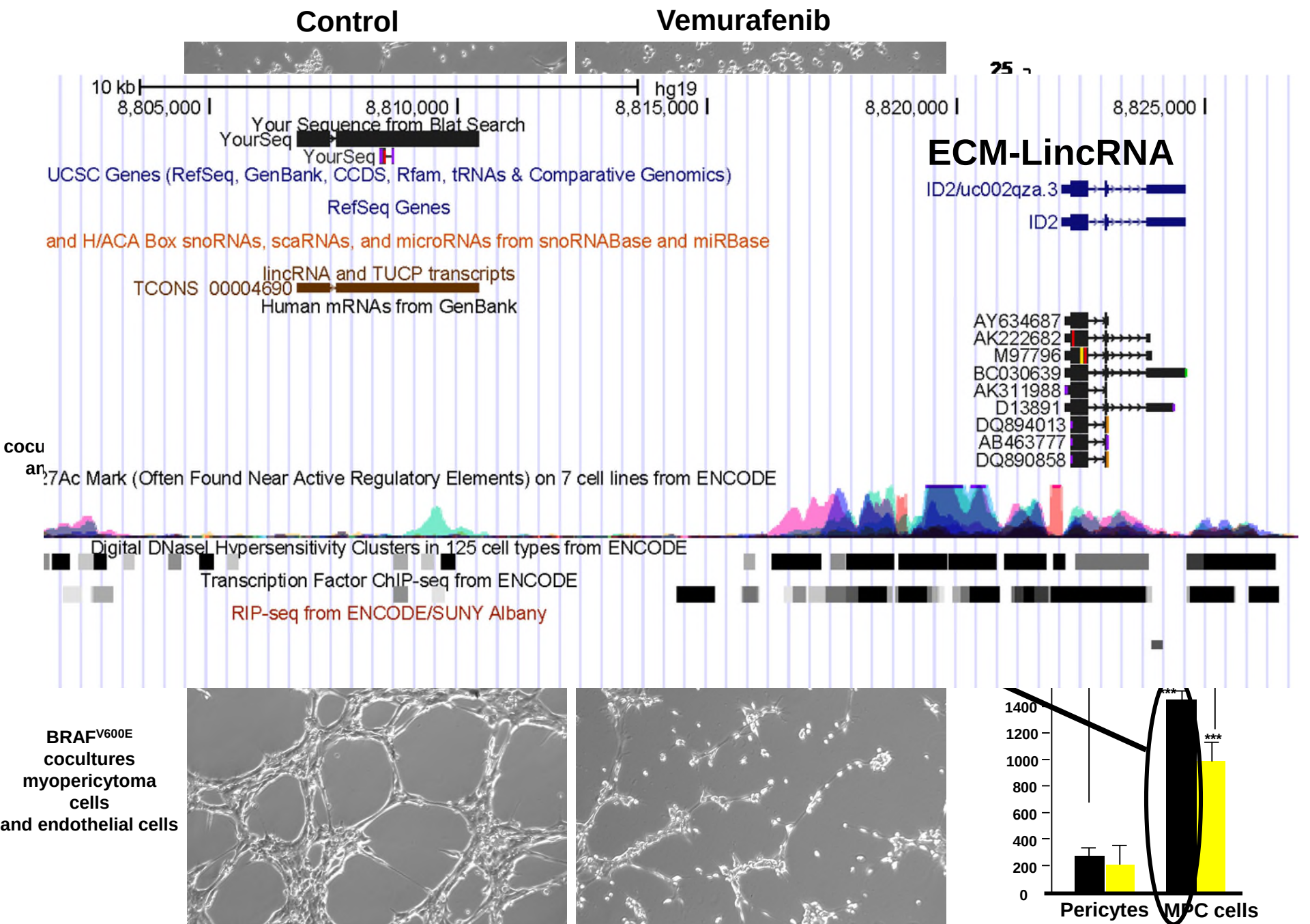








Vemurafenib disrupts *in vitro* angiogenesis induced by BRAF^{V600E}-MPC cells

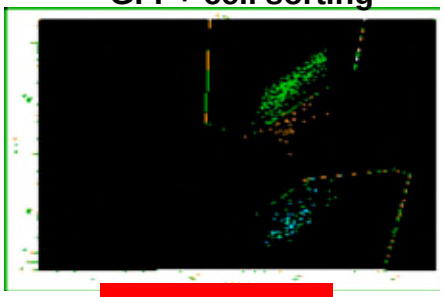


BRAF^{V600E} cocultures myopericytoma cells and endothelial cells

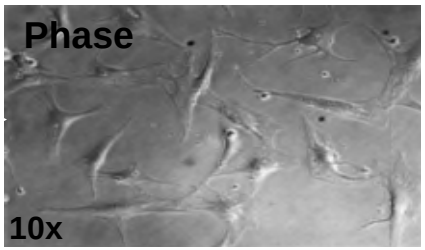
Vemurafenib inhibits viability of BRAF^{V600E} human myopericytoma (MPC) cells in MPC patient-derived xenograft mice

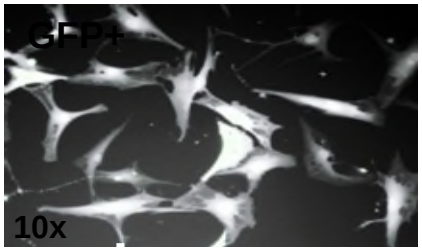
Transduction of GFP+ vector into BRAF^{V600E}-MPC cells

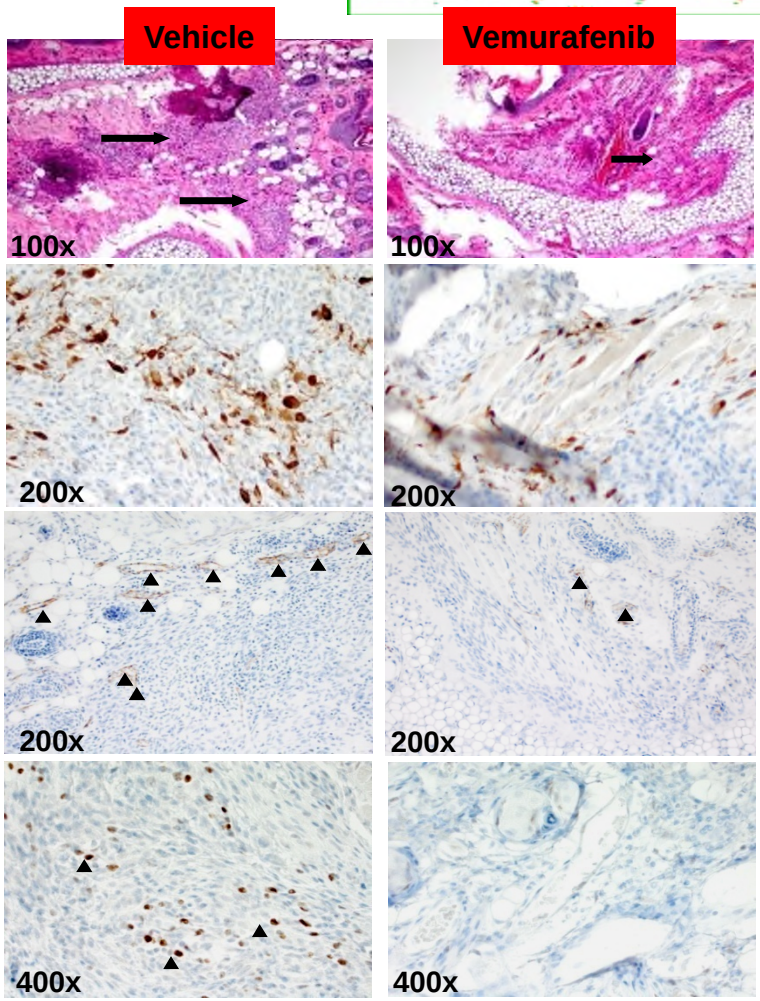
GFP+ cell sorting

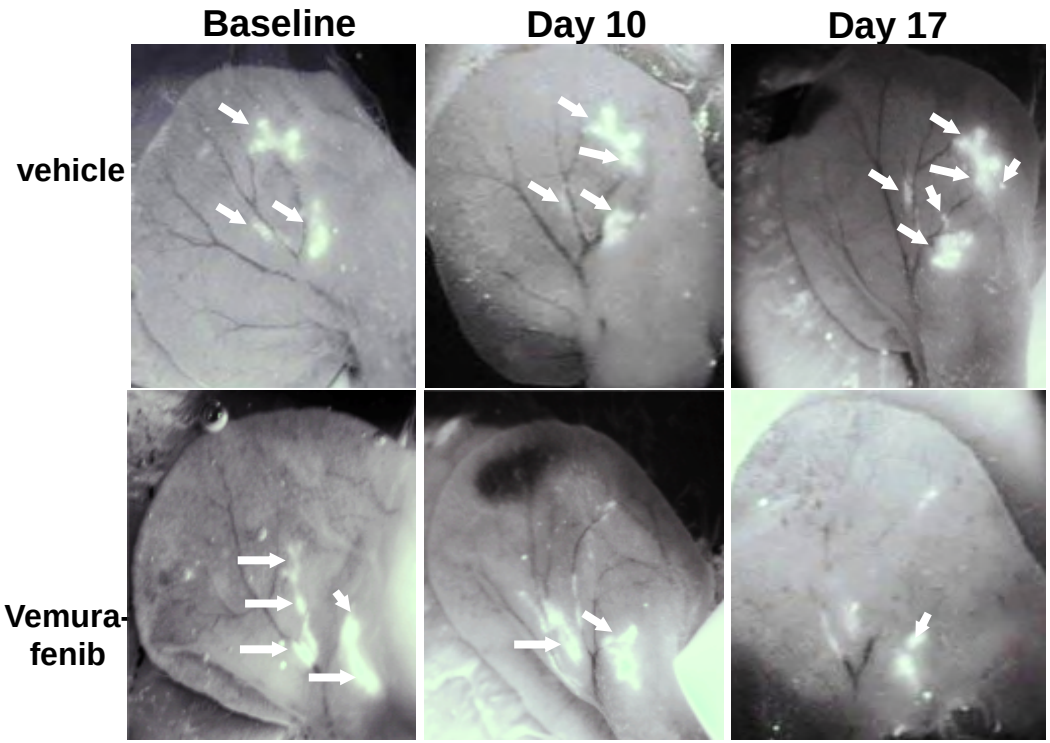


GFP+ thyroid MPC cells with BRAF^{V600E}



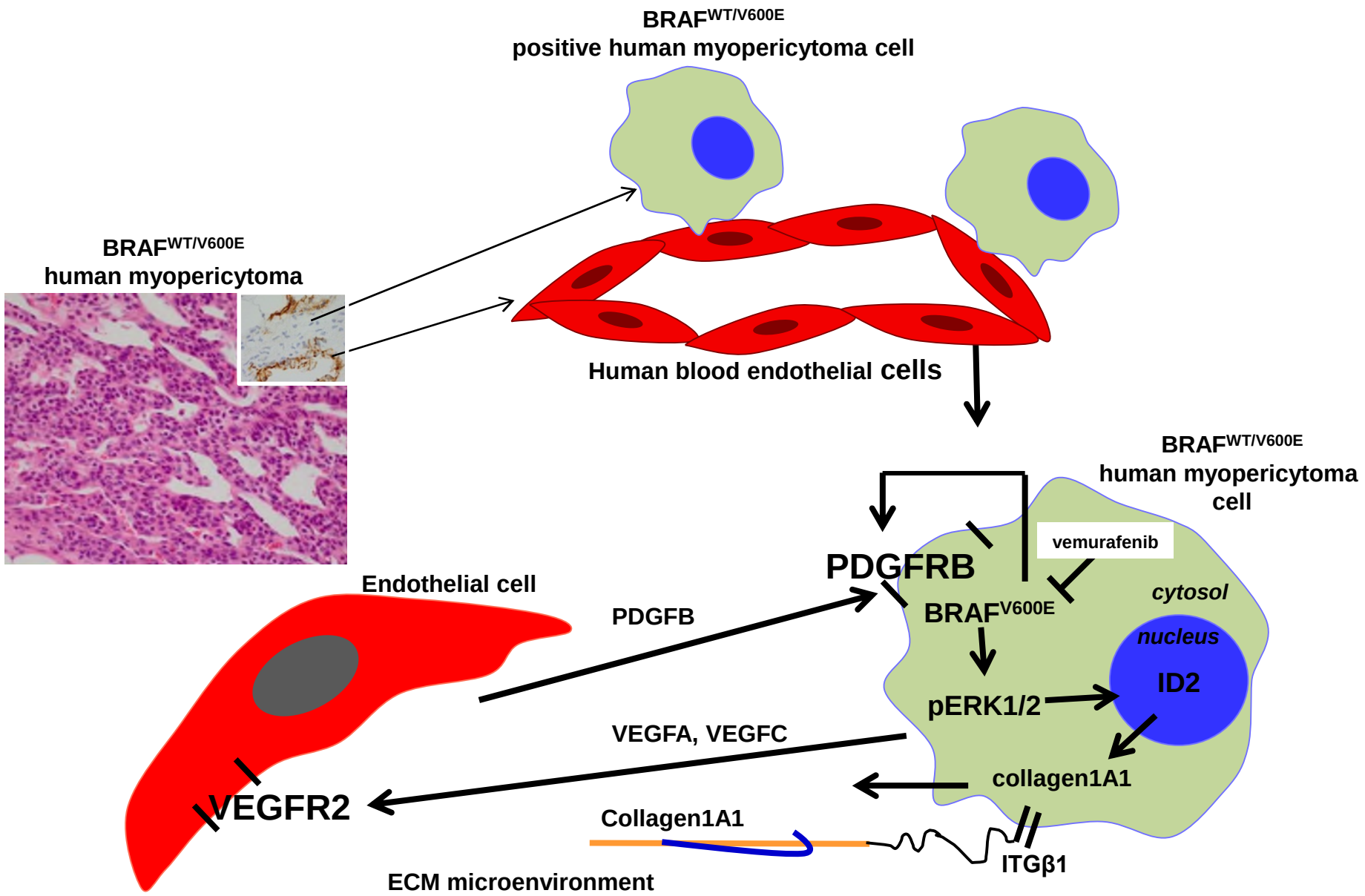






Sadow P….and Nucera C., JNCI 2014

Pericyte-derived tumors in the thyroid harbor the $BRAF^{V600E}$ mutation: a novel tumor microenvironment model

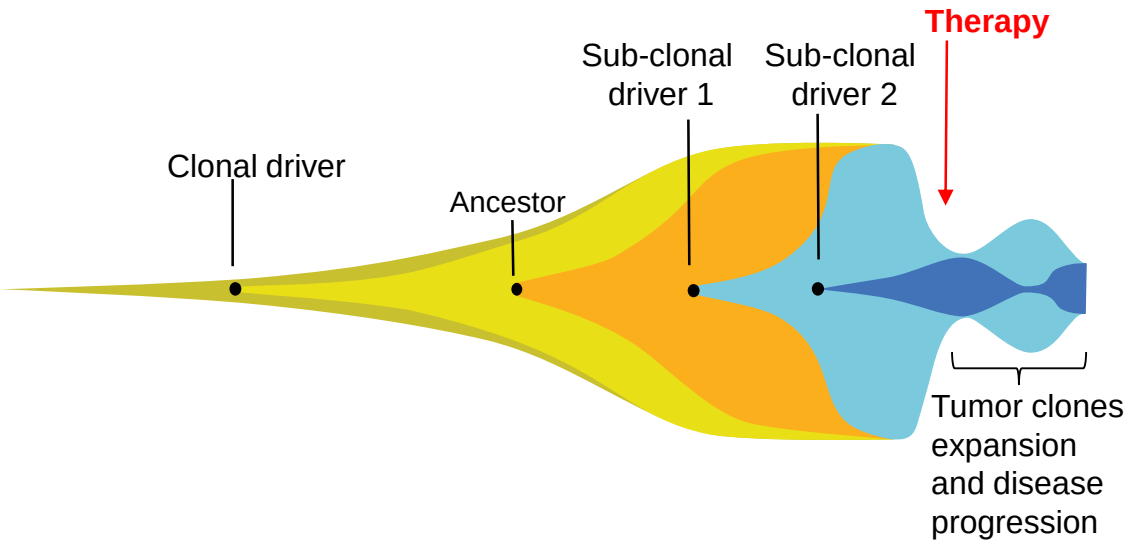


Sadow P….and Nucera C., JNCI 2014

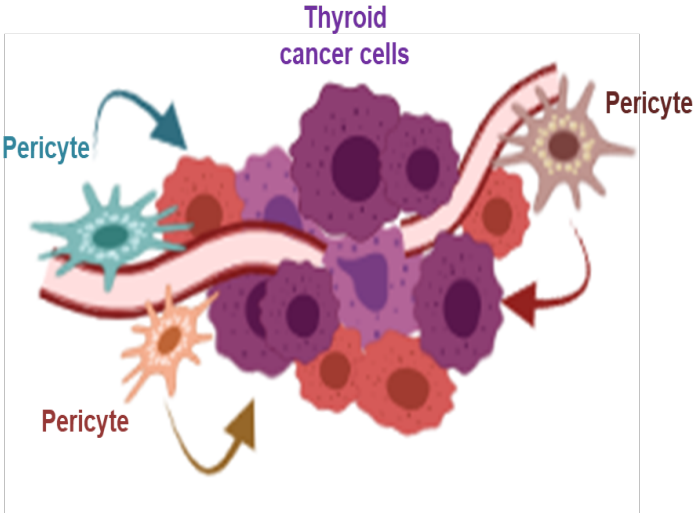
Take-home messages

- Intra-tumor heterogeneity and the strategic skills of tumor cells to evolve may be a major challenge to the implementation of precision anti-cancer medicine.
- Driver mutations (e.g. *BRAF*^{V600E}) are clonal but the presence of copy number variations may be subclonal and resistance mechanisms can evolve rapidly.
- Understanding of the genomic complexity layers (coding and non-coding) by clonal dissection will allow the development of more robust therapeutic strategies.
- Degree of pericyte abundance may be an attractive prognostic marker in assessing pharmaco-therapeutic options.

Cartoon of tumor cell populations defined as clonal or subclonal (each different color represents a cell population)



Microenvironment
paracrine communication between thyroid cancer cells and pericytes



Thank you!