VII SIMPOSIO GETTHI

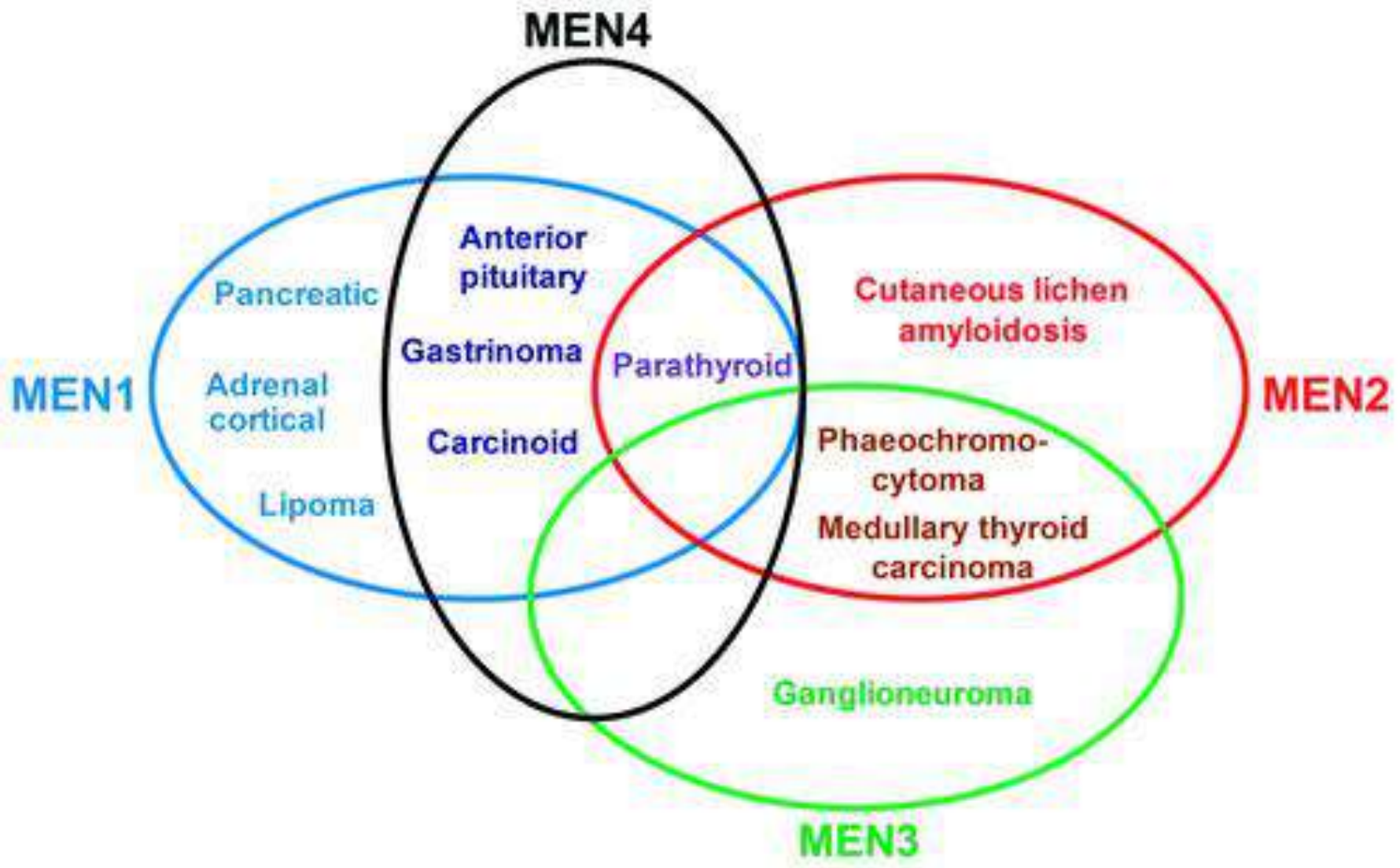
Sesión 1: Del síndrome Hereditario a la diana terapéutica

GETTHI
Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

4 de noviembre de 2021 - *Formato virtual*

Título: Síndrome de Neoplasia Endocrina Múltiple. Bases moleculares y oportunidades terapéuticas

Ponente: Mercedes Robledo


MEN4
MEN1
MEN2
MEN3
Pancreatic
Anterior pituitary
Gastrinoma
Parathyroid
Adrenal cortical
Carcinoid
Lipoma
Cutaneous lichen amyloidosis
Phaeochromo-cytoma
Medullary thyroid carcinoma
Ganglioneuroma

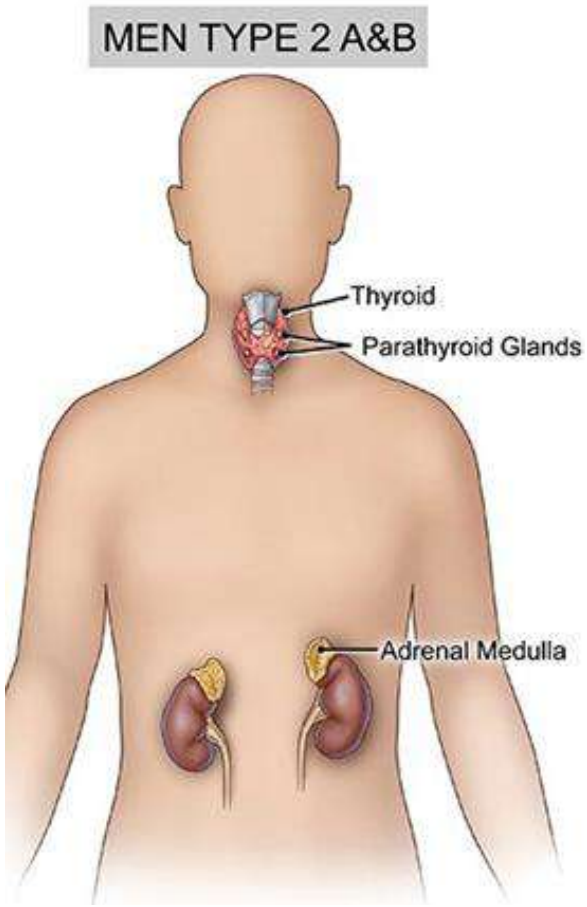


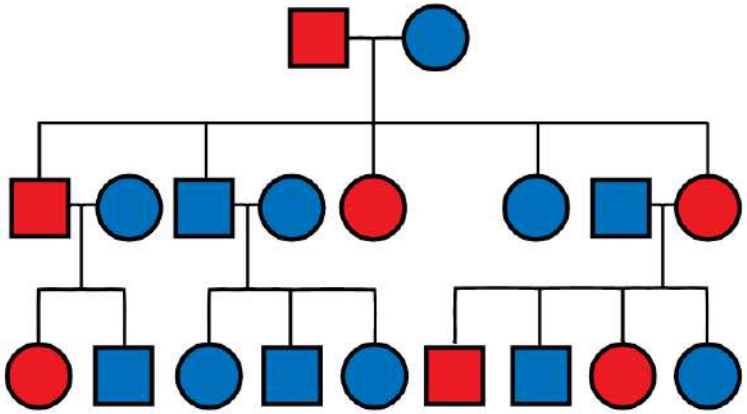
Table 1 Multiple endocrine neoplasia type 2A and type 2B phenotypic characteristics and lifetime risk of development.

	Risk of medullary thyroid carcinoma	Pheochromocytoma	Primary hyperpara-thyroidism	Other extra-endocrine signs
MEN2A	90–100%	0–50% (risk depends on genotype)	0–20% (risk depends on genotype)	<5% (Hirschsprung disease, Cutaneous lichen amyloidosis)
MEN2B (M918T, A883F, tandem mutations)	100%	50% (risk depends on genotype)	0%	100% Gastrointestinal Ophthalmological Skeletal Manifestations Mucosal neuromas

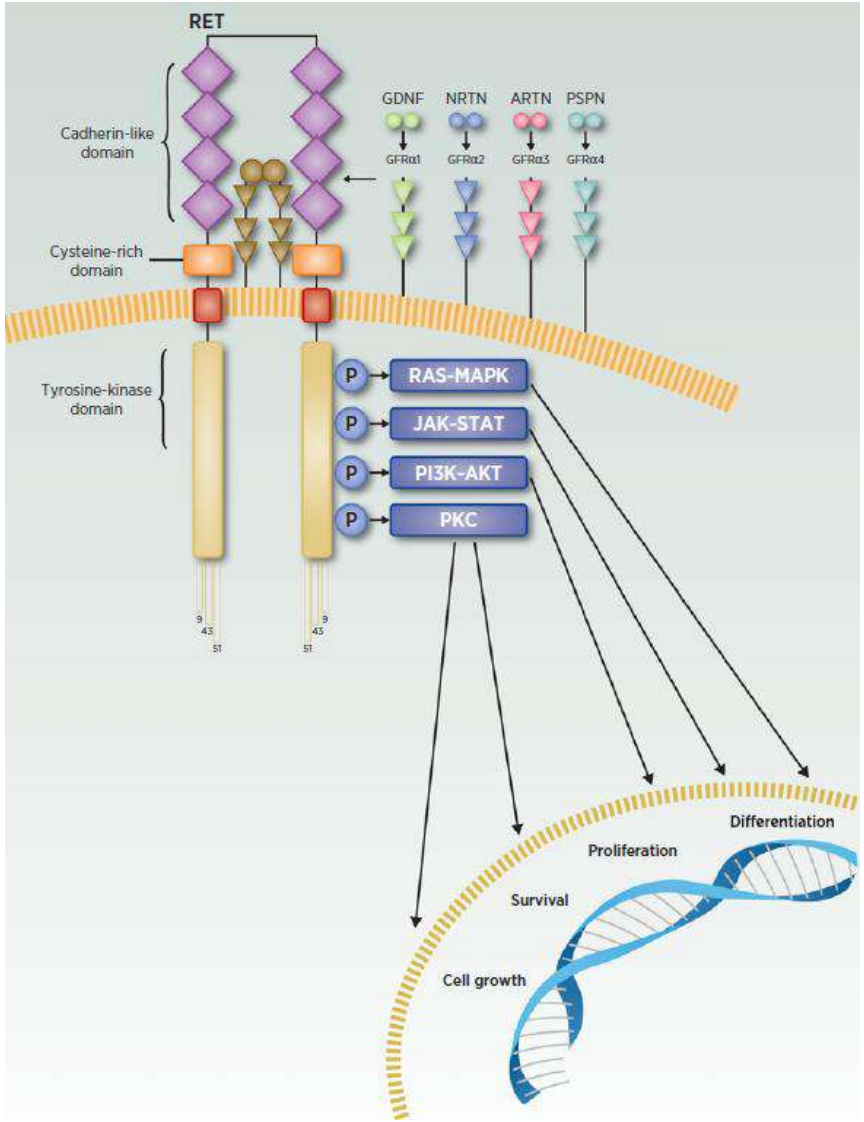
Castinetti F, et al. *Endocr Relat Cancer. 2018 Feb;25(2):T29-T39.*

CMT: 25% hereditary; 75% sporadic
PPGL: 40% hereditary; 40% sporadic; 20% unknown
PHPT: 10-15% hereditary

Dominant inheritance



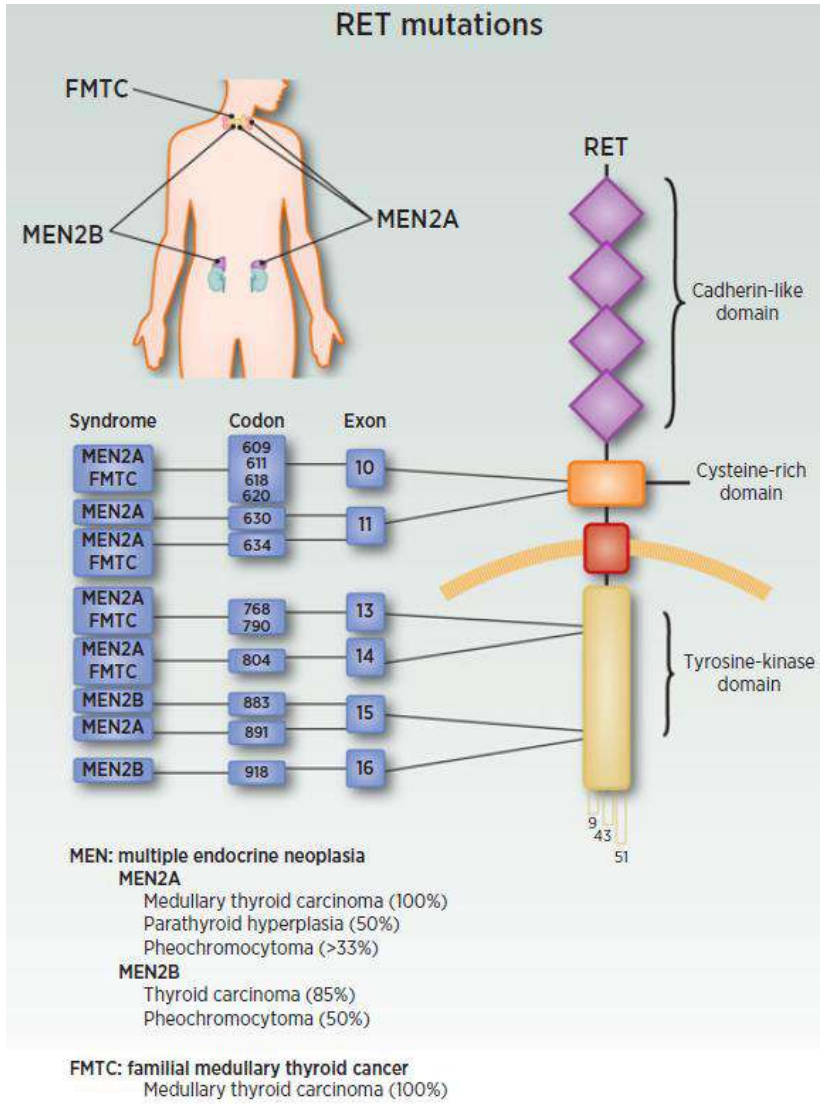
Caused by germline mutations in *RET*
(rearranged during transfection)



RET (located at chromosome 10q11.21) encodes a TK receptor.

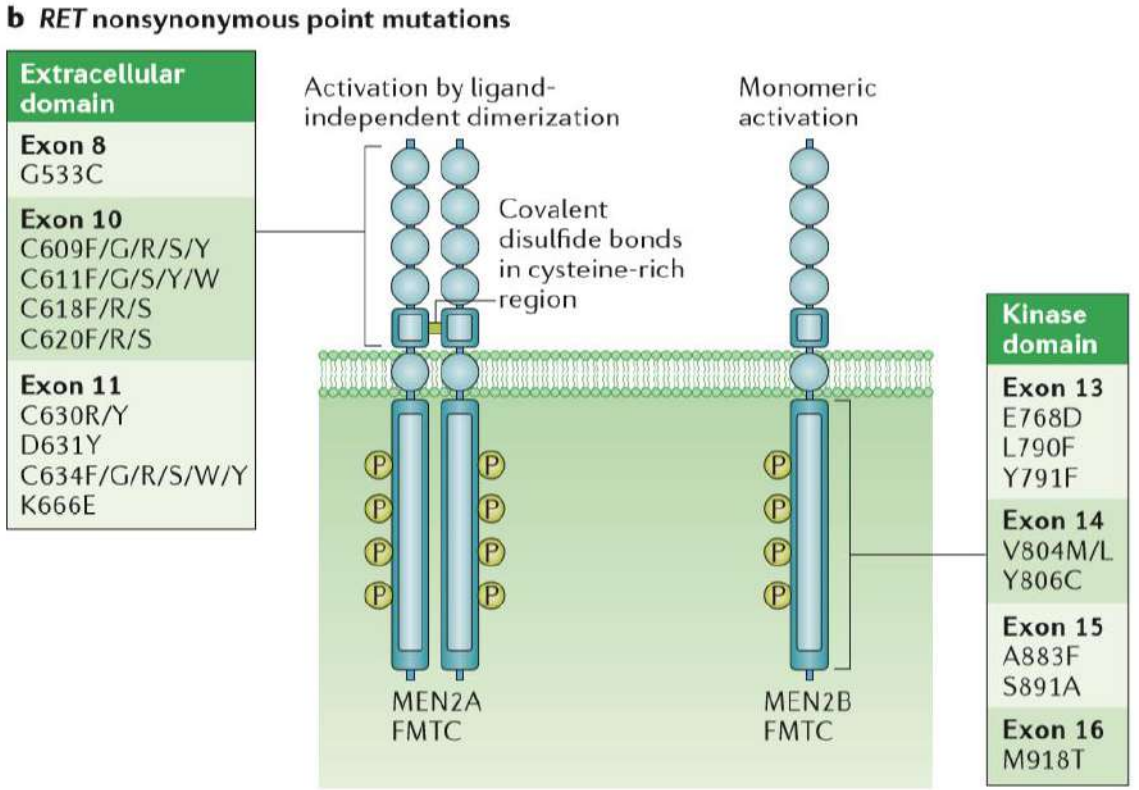
Oncogenic activation mainly in two different ways: (i) chromosomal rearrangement giving rise to chimeric *RET* fusion genes and (ii) **somatic or germline gain-of-function mutations** → constitutive activation of *RET*.

Belli C, et al. *Clin Cancer Res. 2020 Dec 1;26(23):6102-6111.*



Belli C, et al. *Clin Cancer Res. 2020 Dec 1;26(23):6102-6111*.

Mutation effect



Drilon A, et al. *Nat Rev Clin Oncol. 2018 Mar;15(3):151-167*;

Risk according to the specific mutation.

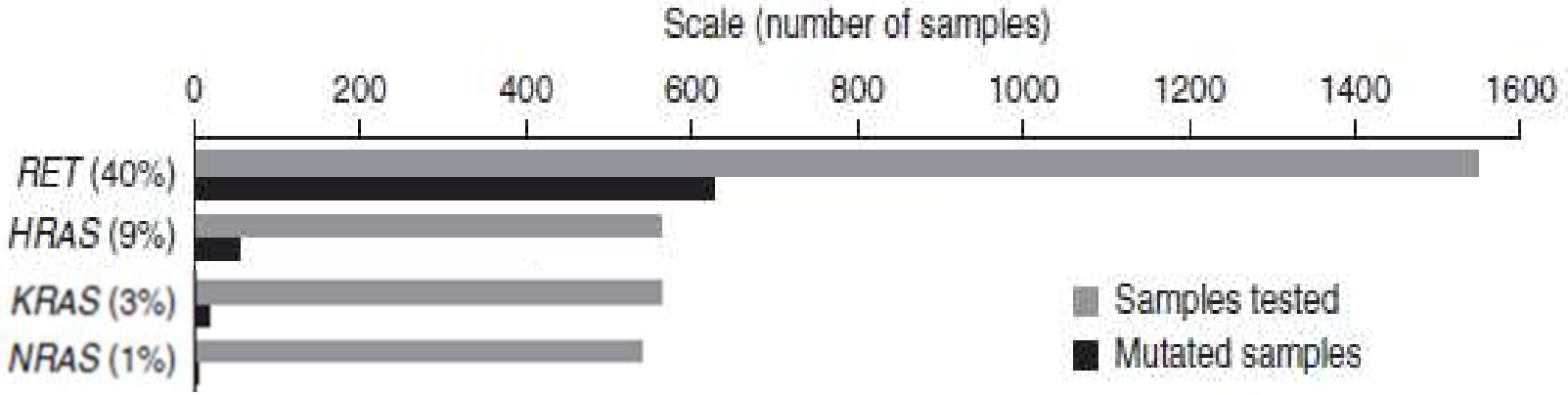
RET mutation	Exon	MTC risk level[a]	Incidence of PHEO[b]	Incidence of HPTH[b]	CLA[c]	HD[c]
G533C	8	MOD	+	-	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C611F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618F/R/S	10	MOD	+/++	+	N	Y
CF20F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	N	N
V804M	14	MOD	+	+	Y	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N

[a]Risk of aggressive MTC: MOD, moderate; H, high; HST, highest; MTC, medullary thyroid carcinoma; PHEO, pheochromocytoma; HPTH, hyperparathyroidism; CLA, cutaneous lichen amyloidosis; HD, Hirschsprung's disease; [b]incidence of PHEO and HPTH; [c]Y, positive occurrence; N, negative occurrence: +=~10%, ++=~0–30%, +++=~5–%.

Presymptomatic genetic testing → prophylactic or early interventions before dissemination of the disease.

Samuel A Wells Jr. *Endocrine-Related Cancer (2018) 25, T1–T13.*

- **25%** of MTC are **hereditary** associated with MEN2 syndrome (***RET* germline mutations**).
- The remaining **75%** are classified as **sporadic**: can be related to ***RAS* or *RET* somatic mutations (mostly mutually exclusive)**



Moura MM, Cavaco BM, Leite V. *Endocr Relat Cancer. 2015 Oct;22(5):R235-52.*

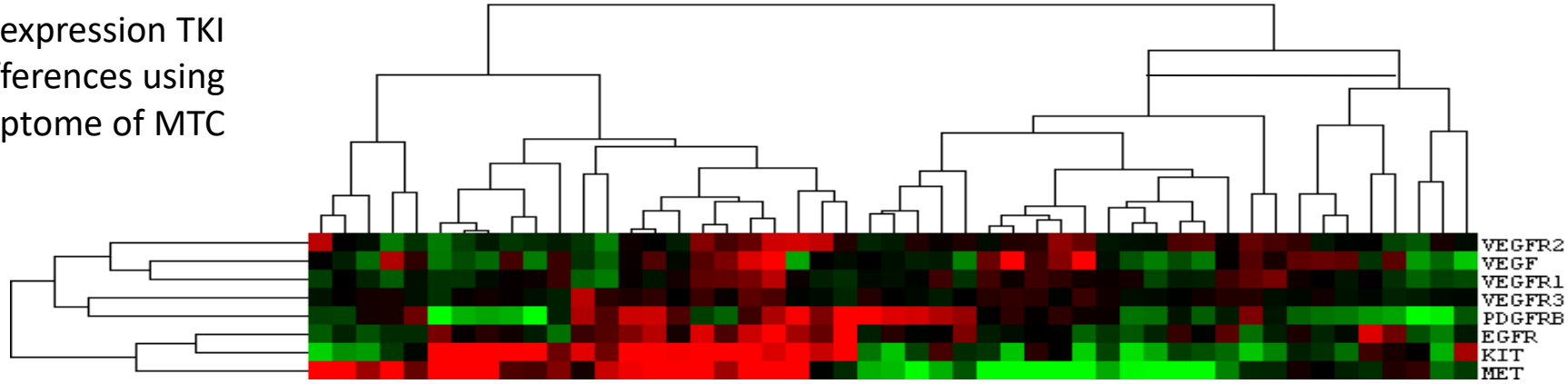
Multikinases inhibitors, originally developed to target conserved regions of other kinases have also shown **efficacy against RET**.

MKIs	Study phase	All pts	Treatment group	ORR (%)[a]	mPFS (mos.)	mOS (mos.)	TRAEs all grades (%)[b]
			Thyroid cancer				
Sorafenib (68)	II	21	Sorafenib	1/15 (6)	17.9	nr	HFSR 19/21 (90) Rash (non-HFSR) 18/21 (86)
Lenvatinib (69)	II	59	Lenvatinib	21/59 (36)	9.0	16.6	Diarrhea 44/59 (75) Proteinuria 35/59 (59)
Sunitinib (70)	II	71	Sunitinib	19/71 (27)	na	na	Asthenia/fatigue 59/71 (83) Mucosal AE 46/71 (65)
Dovitinib (71)	II	40	Dovitinib	8/39 (20)	5.4	nr	Diarrhea 21/39 (54) Anorexia (36)
Motesanib (72)	II	91	Motesanib	2/91 (2)	12	na	Thyroid dysfunctions 76/91 (83) Diarrhea 37/91 (41) Fatigue 37/91 (41)
Vandetanib (66)	III	331	Vandetanib	104/231 (45)	30.5	na	Diarrhea 130/231 (56) Rash 104/231 (45)
			Placebo	13/100 (13)	19.3		
Cabozantinib (64, 65, 67)	III	330	Cabozantinib	58/208 (28)	11.2	26.6	Diarrhea 135/214 (63) PPE 107/214 (50)
			Placebo	0/104 (0)	4.0	21.1	
			Mutational subgroups				
			Cabozantinib				
			RET MUT+	32/101 (32)	14	–	
			RET MUT–	7/32 (22)	5.8	–	
			RET M918T+	26/77 (34)	14.2	44.3	
			RET M918T–	14/69 (2)	5.8	20.2	
			Placebo				
			RET M^{918T+}	–	–	18.9	
			RET M^{918T-}	–	–	21.5	

Any clue about inter-patient response rate variability?

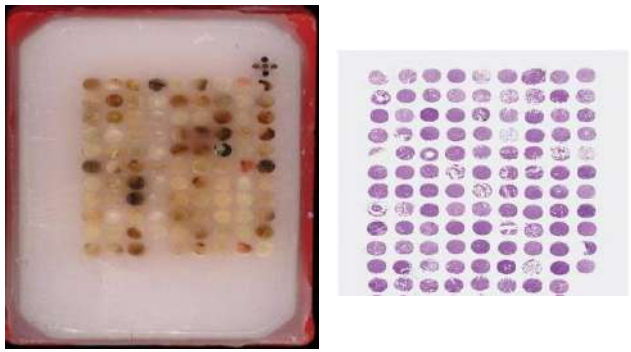
Belli C, et al. *Clin Cancer Res. 2020 Dec 1;26(23):6102-6111.*

Exploring expression TKI receptors differences using transcriptome of MTC

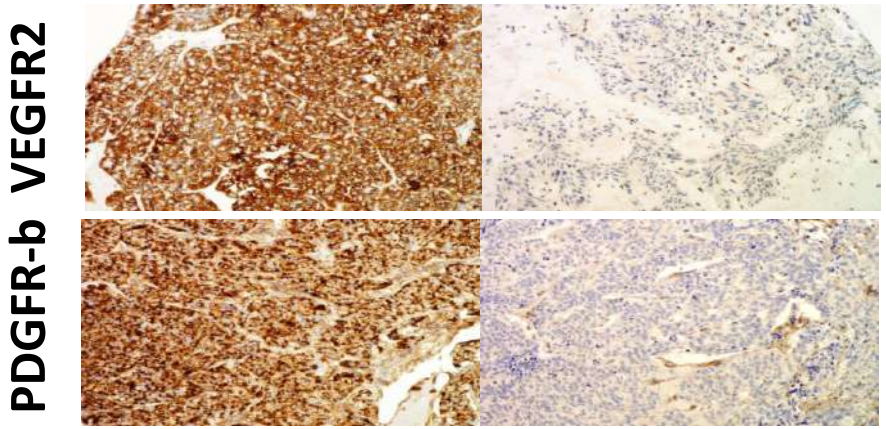


103 primary MTC (genetically characterized)

Tissue arrays



IHC of 8 key proteins



Rodriguez-Antona, C et al. *Endocr Relat Cancer. 2013 Jul 12;20(4):611-9.*

The driver mutation can affect the likelihood of benefiting from a particular TKI therapy

	RAS vs *RET*			WT vs *RET*			WT vs *RAS*		
Proteins[$]	*RAS*	*RET*	*p*-value	WT	*RET*	*p*-value	WT	*RAS*	*p*-value
VEGF	2/12 (17%)	15/52 (29%)	0.49	9/13 (69%)	15/52 (29%)	**0.011**	9/13 (69%)	2/12 (17%)	**0.0082**[*]
PDGFRB	0/13 (0%)	21/53 (40%)	**0.0060**[*]	2/12 (17%)	21/53 (40%)	0.19	2/12 (17%)	0/13 (0%)	0.22
VEGFR1	6/10 (60%)	13/37 (35%)	0.28	6/13 (46%)	13/37 (35%)	0.52	6/13 (46%)	6/10 (60%)	0.68
VEGFR2	4/10 (40%)	22/39 (56%)	0.48	10/13 (77%)	22/39 (56%)	0.19	10/13 (77%)	4/10 (40%)	0.10
VEGFR3	1/14 (7%)	31/53 (59%)	**0.00062**[*#]	5/12 (42%)	31/53 (59%)	0.35	5/12 (42%)	1/14 (7%)	0.065
MET	0/12 (0%)	12/40 (30%)	**0.047**	4/14 (29%)	12/40 (30%)	0.99	4/14 (29%)	0/12 (0%)	0.10
	RAS vs *RET* [C634]			*RAS* vs *RET*[M918T]					
Proteins[$]	*RAS*	*RET* [C634]	*p*-value	*RAS*	*RET*[M918T]	*p*-value			
VEGF	2/12 (17%)	6/24 (25%)	0.69	2/12 (17%)	6/16 (38%)	0.40			
PDGFRB	0/13 (0%)	11/24 (46%)	**0.0032**[*]	0/13 (0%)	6/17 (35%)	**0.024**[*]			
VEGFR1	6/10 (60%)	3/17 (18%)	**0.039**[#]	6/10 (60%)	5/10 (50%)	0.99			
VEGFR2	4/10 (40%)	10/17 (59%)	0.44	4/10 (40%)	6/12 (50%)	0.69			
VEGFR3	1/14 (7%)	16/24 (67%)	**0.00037**[*#]	1/14 (7%)	10/17 (59%)	**0.0067**[*#]			
MET	0/12 (0%)	4/17 (24%)	0.12	0/12 (0%)	5/14 (36%)	**0.042**			

- ***RAS*-related MTC do not express MET and PDGFRB.**
- ***RET*-related express more frequently VEGFR3.**
- **WT MTC express notably more frequently VEGF.**

Rodriguez-Antona, C. et al. *Endocr Relat Cancer.* ***2013*** *Jul 12;20(4):611-9;* **Mancikova *et al.***, *Thyroid 24(8):1251-5, 2014.*

To note: side effects →

Treatment discontinuation rate was 12% with vandetanib and 16% with cabozantinib,
Dose reduction: 35% of patients treated with vandetanib and 79% with cabozantinib.

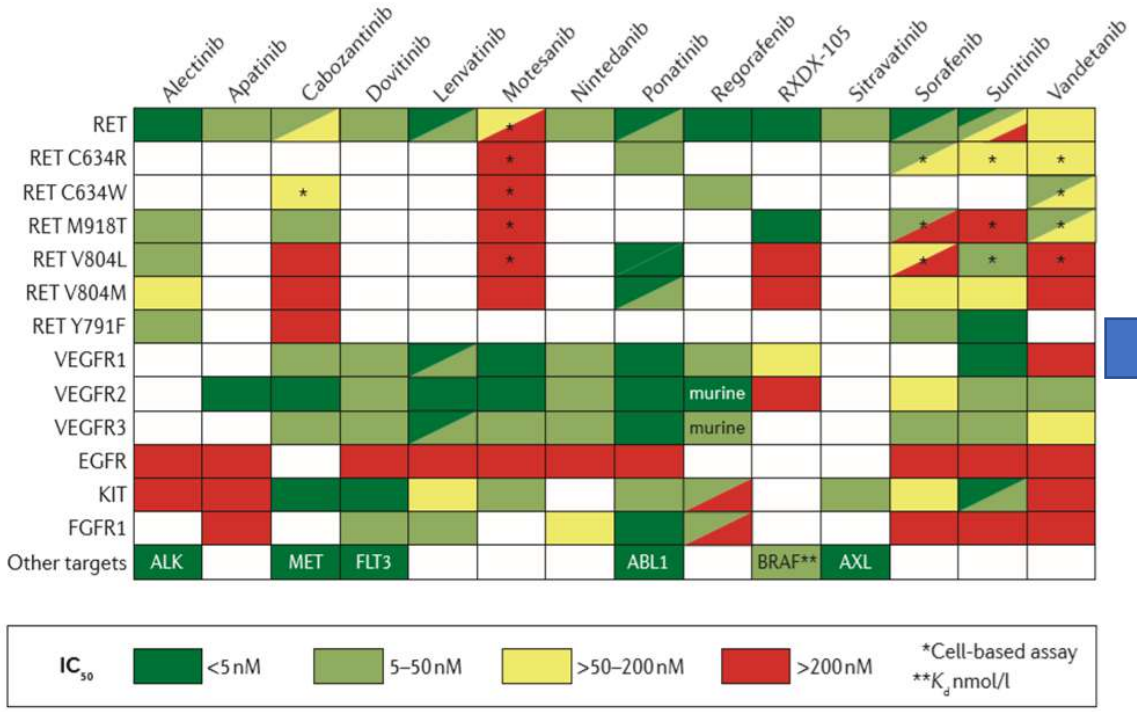


Figure 4 | **Multikinase inhibitor activity against RET and other kinases.** The half-maximal inhibitory concentration (IC_{50}) of select multikinase inhibitors with varying levels of activity against RET are shown. The various colours represent a range of IC_{50} values, from <5 nM to >200 nM. Unless otherwise indicated, the IC_{50} values shown reflect the results of *in vitro* kinase assays. The presence of two or more colours within a given box indicate different IC_{50} values reported in separate publications. A white box indicates that biochemical data are not currently available.

New RET inhibitors: higher specificity

Efstathiadou ZA, et al. *Eur Thyroid J 2021;10:125–139;*
Belli C, et al. *Clin Cancer Res. 2020 Dec 1;26(23):6102-6111.*
Drilon A, et al. *Nat Rev Clin Oncol. 2018 Mar;15(3):151-167;*

New RET inhibitors, selpercatinib and pralsetinib, might **solve off-target toxicity** problems as they inhibit more potently and selectively both wild-type RET and RET+ cancer cell lines in biochemical assays.

Table 3. Clinical trials with new selective *RET* inhibitors in lung and thyroid cancer.

RET inhibitors	Tumor type	All pts	Fusion or mutation types (%)	ORR (%)[a]	TRAEs all grades (%)[b]
Selpercatinib (73)	Thyroid	226	M918T 129/226 (57) Non-M918T 97/226 (43)	Treatment naïve 64/88 (73) Pretreated 38/55 (69)	nr[c]
Pralsetinib (76)	Thyroid	64	M918T 36/64 (56) Non-M918T 28/64 (44)	18/32 (56)	Hypertension 19/64 (30) Neutropenia 15/64 (23)

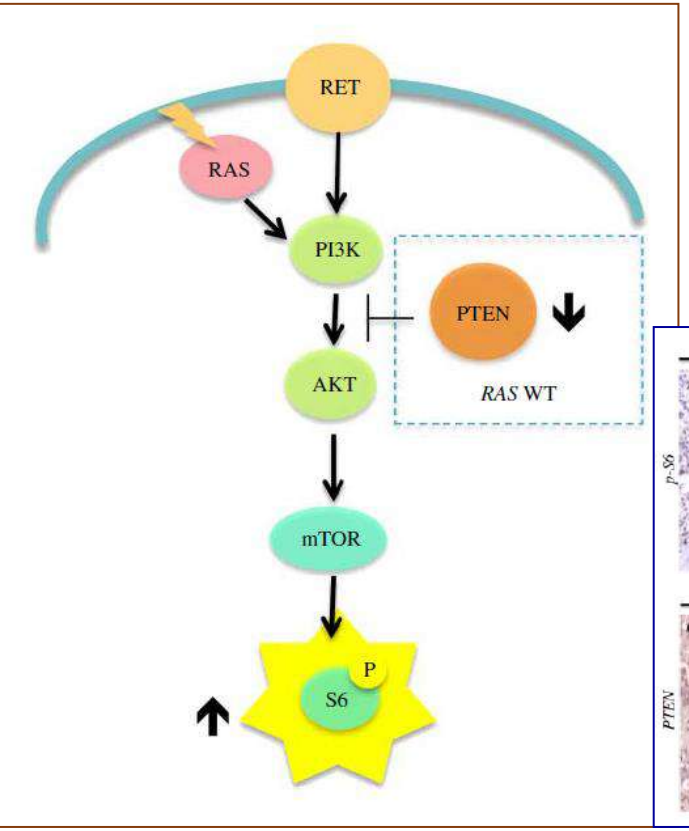
RET alterations have become increasingly more relevant in the clinics. These **new *RET* inhibitors** → improved response rates, more durable disease control, and favorable safety profile compared with MKIs (possibly due to the lack of VEGF Inhibition). **But** these two drugs will not be used in *RET*-negative MTCs.

Again → **mechanisms of acquired resistance*** to first-generation selective RET inhibitors is **not yet fully known**

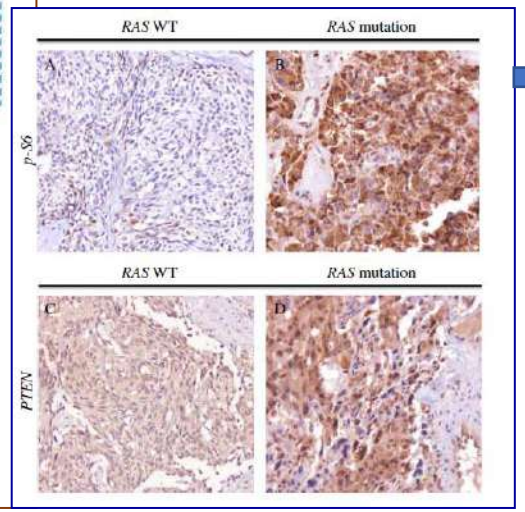
The **next-generation RET inhibitors**: TPX-0046 and BOS172738.

Bartz-Kurycki MA, et al. *Ther Adv Endocrinol Metab 2021, Vol. 12: 1–13;* **Belli C, et al.** *Clin Cancer Res. 2020 Dec 1;26(23):6102-6111*; **Subbiah V, et al.** *Cancer Discov 2018;8: 836–49*.

Alternatives? → Combination **therapy based on the biological knowledge**



- Activation of the mTOR pathway has been demonstrated in MTC (particularly strong in MTC metastases).



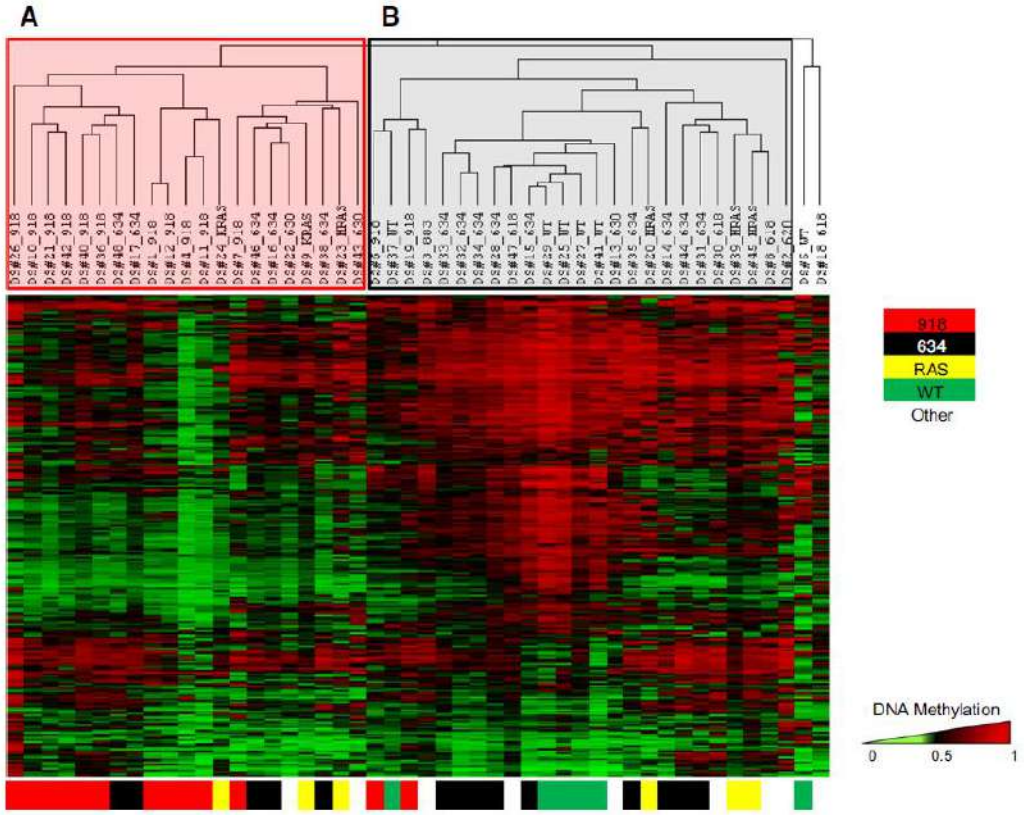
p-S6 high expression in *RAS*-related MTC vs WT- *RAS* (*P*=0.007)

p-S6 expression can be used as indicator of increased metastatic capacity of MTC, as well as a potencial predictive biomarker for mTOR inhibitors response.

Rapa I, et al. *J Clin Endocrinol Metab* ***2011****;96:2146–53;* **Tamburrino, A et al**. *Clin Cancer Res* ***2012****;18:3532-3540*; **Lyra I, et al.** *Eur J Endocrinol* ***2014****; 171: 633-640* ; **Pennelli G, et al.** *Human Pathology 2015; 46 50–57*.

Alternatives? → Combination **therapy based on the biological knowledge**

Based on 48 frozen MTCs genetically characterized



Activation of JAK/STAT signaling pathway linked to p.M918T mutation

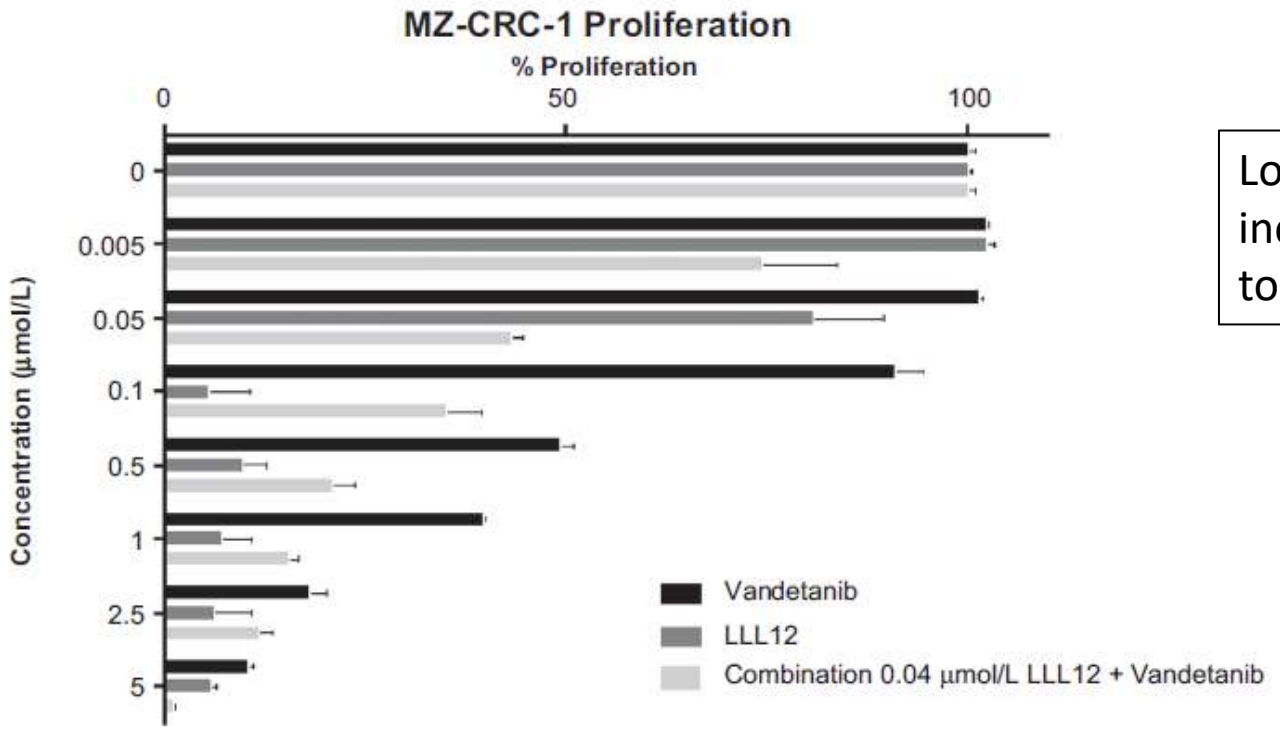
Activation of STAT3 is associated with a **worse prognosis** due to its role in uncontrollable proliferation, inflammation and modulation of microenvironment.

Thus, STAT3 is a very **attractive molecule for targeted therapies**.

Thomas SJ, et al. *Br J Cancer 2015;113:365–71*.
Debnath B, et al. *J Med Chem 2012; 55:6645–68*.

Mancikova V et al. *Clin Cancer Res; 2017 Mar 1;23(5):1334-1345.;*

Our **aim** was **to know if this activation could be relevant for treatment response**, and then we use STAT3 inhibitors commercially available.



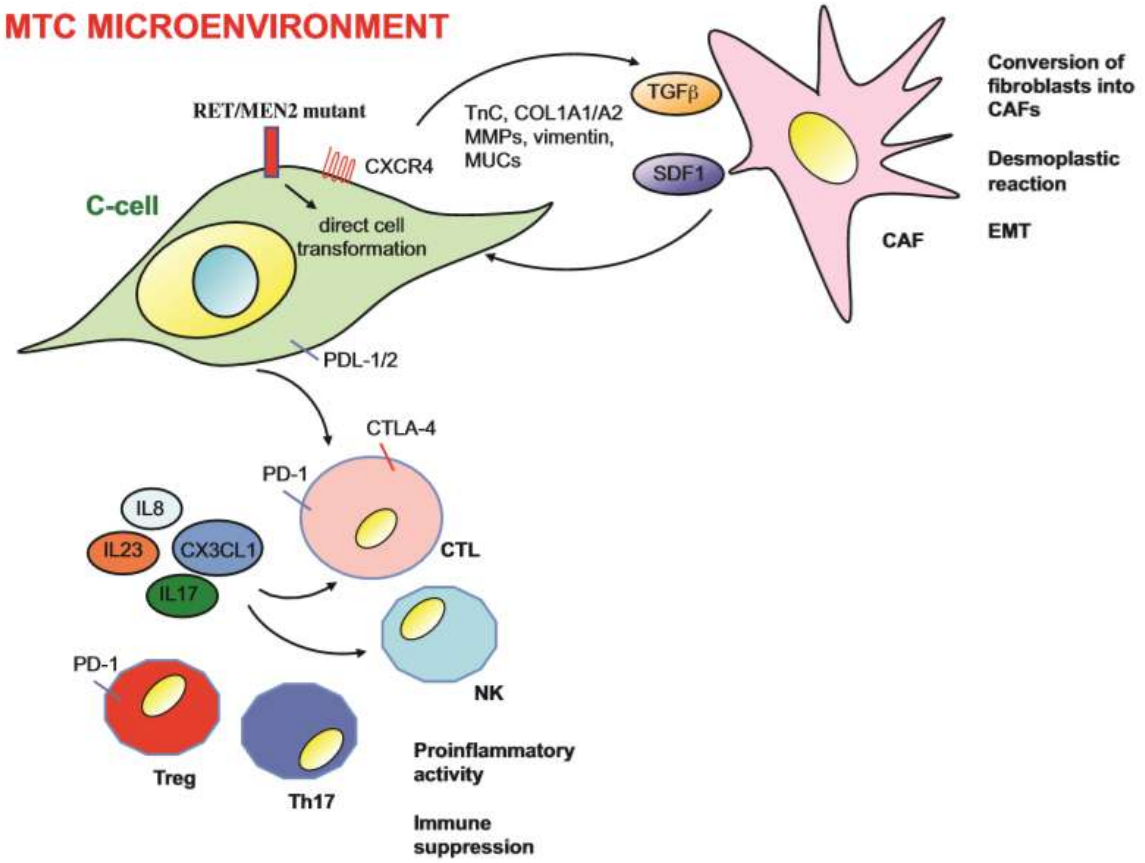
Low doses of the inhibitor of pSTAT3 increased the sensitivity of MTC cells to vandetanib tratment.

Mancikova V et al. *Clin Cancer Res; 2017 Mar 1;23(5):1334-1345;*

Alternatives? → Combination **therapy based on the biological knowledge**

Beyond tumor cells →TME.

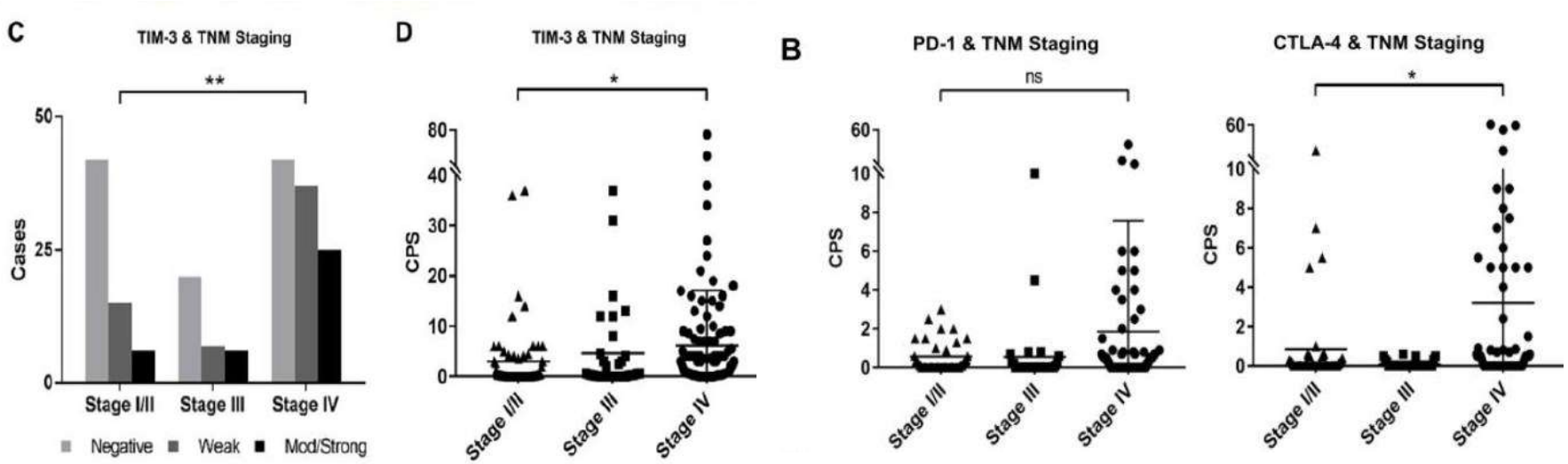
The activation of the **immune-inflammatory transcriptional program depends** on the signaling pathway activated and thus, **on the mutation**.



Castellone MD, Melillo RM. *Endocr Relat Cancer. 2018 Feb;25(2):T105-T119*;

200 patients were enrolled

tumor-infiltrating leukocytes (TILs),
PD-1, CTLA-4, TIM-3, LAG-3, TIGIT



In the setting of advanced MTCs, single or combined immunotherapy including TIM-3, PD-1/PD-L1 or CTLA-4 blockade may be potential therapeutic approaches

Xiao Shi, et al. *JCEM 2021, 106: 120–132*

Lack of **MTKs response is multifactorial** and influenced by the specific target mutation, the off-target inhibition, intrinsic resistance, pathway reactivation, and TME.

The deeper biological knowledge of mechanisms involved in these events will facilitate **combined and personalized treatment**.