GETTHI

Grupo Español de Oncología Transversal
y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 1: Del síndrome Hereditario a la diana terapéutica

4 de noviembre de 2021 - *Formato virtual*

EL PROTOONCOGEN RET

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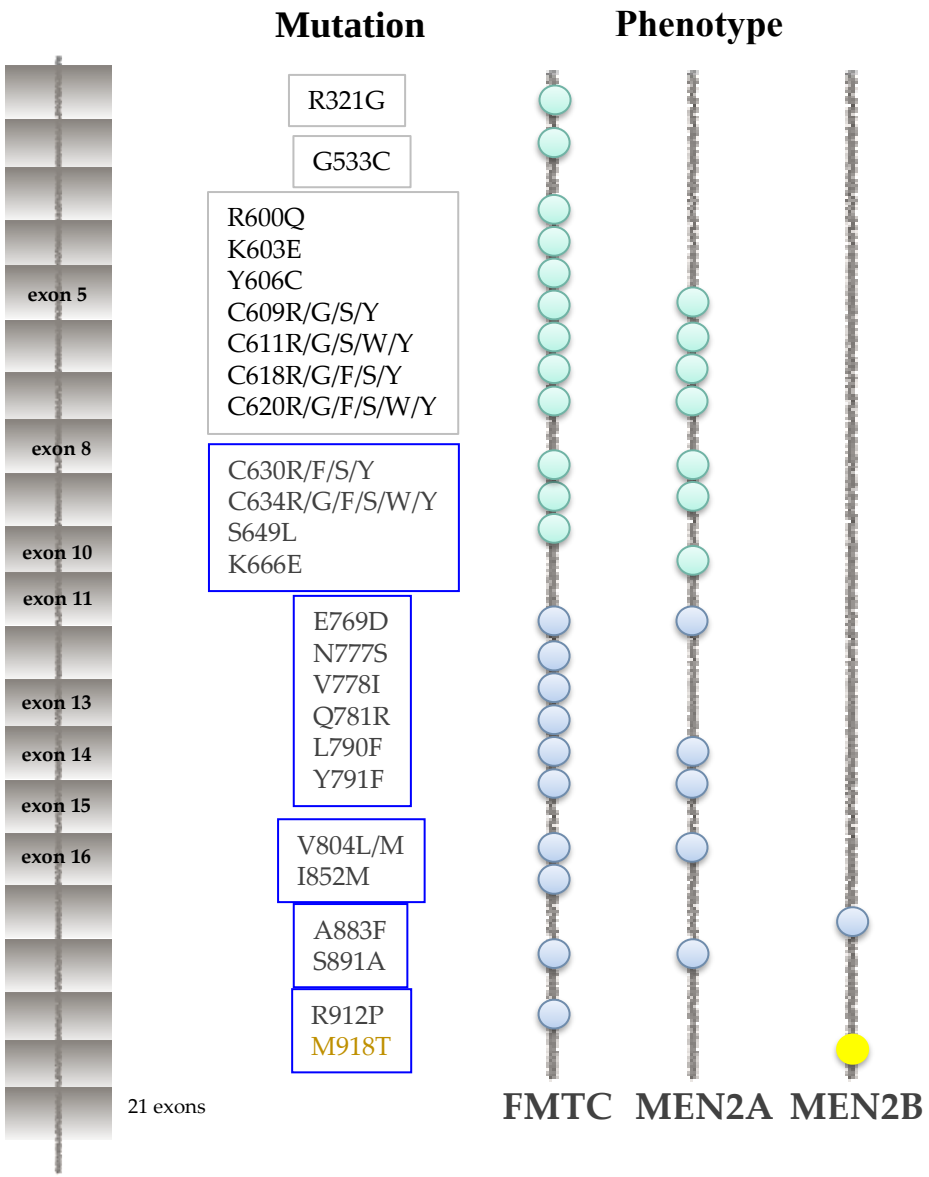
DISCLOSURES

Personal confilcts of interest _ Scientific Consultancy Role (speaker and advisory role) and travel grant: *IPSEN, Pfizer, Roche, Bayer, Sanofi, Janssen, Lilly, Astellas, Eisai, Adacap, Novartis, BMS.*

Participation in Clinical trials: *Roche, BMS, MSD, Pfizer, Novartis, IPSEN, Exelixis, Astrazeneca-Medimmune, Janssen, Lilly, Eisai, Astellas.*

Research support: *Roche, Pfizer, IPSEN.*



STRUCTURE

EXTRACELLULAR PORTION: 4 cadherin-like and one cysteine-rich domains

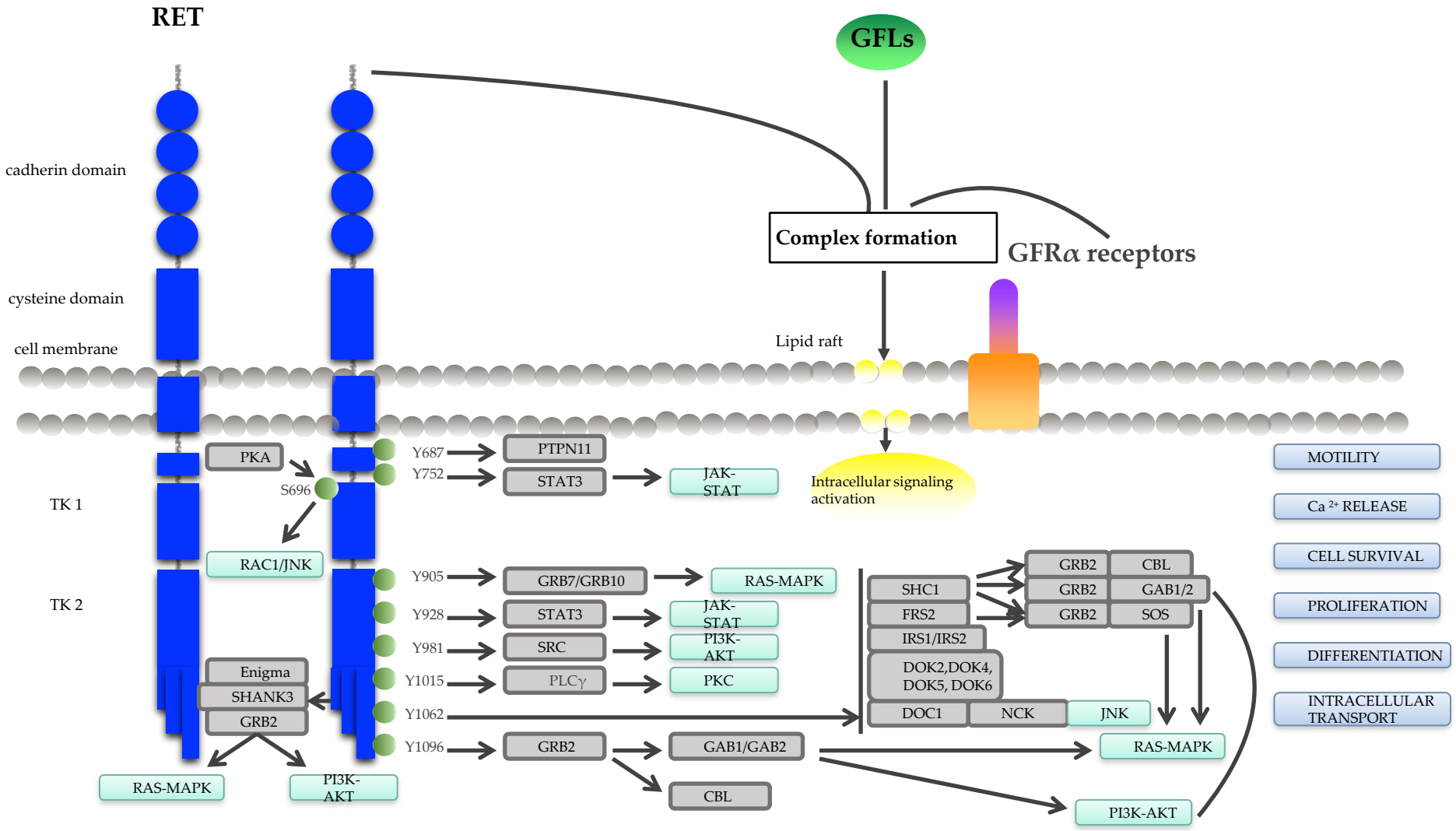
TRANSMEMBRANE PORTION

INTRACELLULAR PORTION: contains the **tyrosine kinase domain** (TKD) that is split into two subdomains. It is followed by a **C-terminal tail** subject to alternative splicing generating different isoforms, the most abundant being RET9 and RET51

Moura, M., et al. JCEM 2011; 96: 863-868
Agrawal, N., et al. JCEM 2013; 98: 364-369
Ciampi, R., et al. Tyroid 2013; 23: 1-4

FUNCTION

GFLs (GDNF family ligand): GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN)



De Groot, et al. RET as therapeutic Target in Neuroendocrine Tumors. Endocrine Reviews 2006; 27: 535-560
Mulligan, L.M. RET revisited: expanding the oncogenic portfolio. Nature Reviews 2014; 14: 173-186

FUNCTION

KIDNEY DEVELOPMENT (and TESTES GERM CELLS) → RET INACTIVATION → RENAL AGENESIS OR SEVERE HYPODYSPLASIA IMPAIRED SPERMATOGENESIS

NERVOUS SYSTEM DEVELOPMENT → ENTERIC NERVOUS SYSTEM → RET INACTIVATION → HIRSCHSPRUNG'S DISEASE COLONIC AGANGLIOSIS

NERVOUS SYSTEM DEVELOPMENT → VENTRAL MIDBRAIN DOPAMINERGIC NEURONS → RET INACTIVATION → DOPAMINERGIC NEURON DEVELOPMENT OR MAINTENANCE. PARKINSON´S DISEASE

NERVOUS SYSTEM DEVELOPMENT → MOTONEURONS → RET INACTIVATION → MOTONEURON SURVIVAL AND CONNECTIVITY

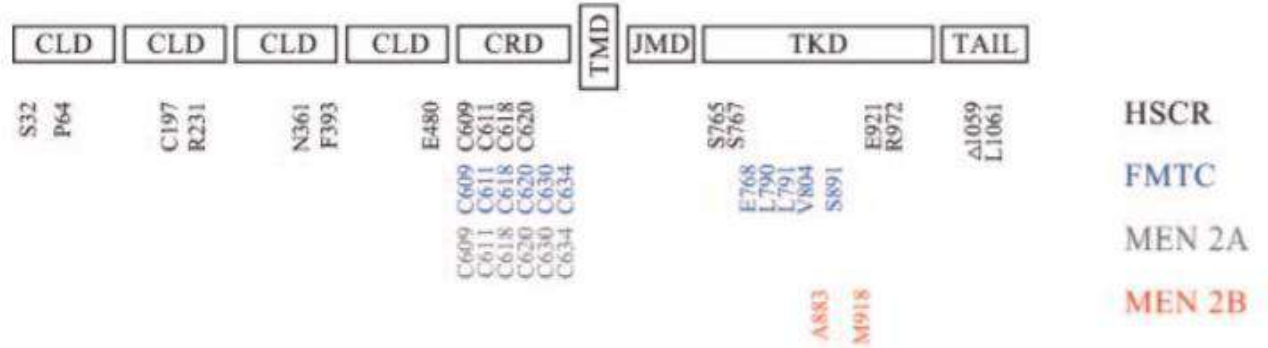
ADRENAL CHROMAFFIN CELLS AND THYROID C CELLS → RET INACTIVATION → REDUCTION IN THYROID C CELLS

Ibañez C. Cold Spring Harbor Laboratory Press 2013

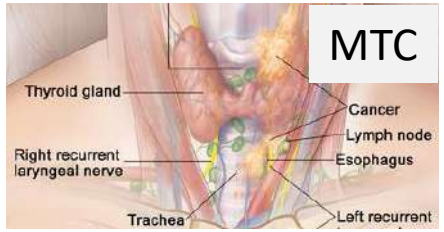
RET ONCOGENIC CONVERSION IN HUMAN NEOPLASMS

GERMLINE

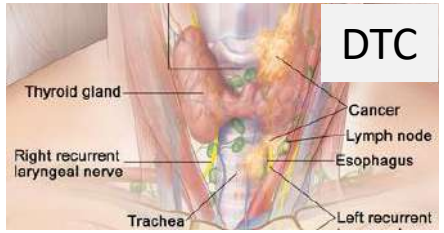
SOMATIC



RET mutations



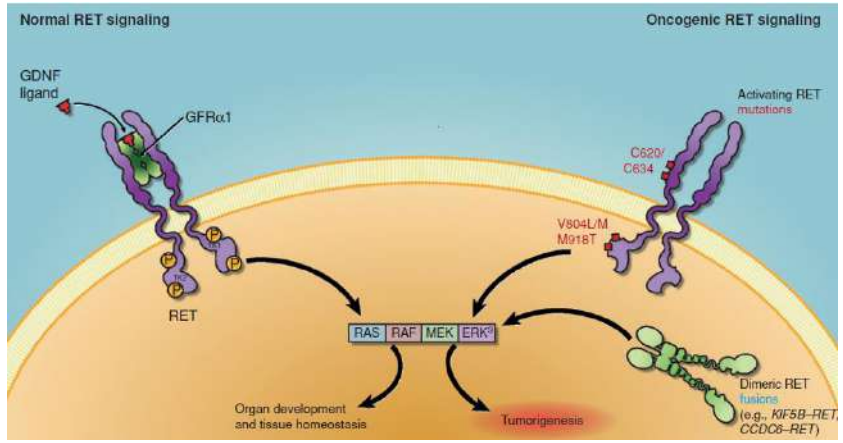
RET fusions



Few other tumors:
BRCA (breast invasive carcinoma),
CMML (Chronic myelomonocytic leukaemia),
CRC (colorectal carcinoma),
IC (intraductal carcinoma of the salivary gland),
IFS (infantile fibrosarcoma),
IM (infantile myofibromatosis),
IMA (invasive mucinous lung adenocarcinoma),
LPF (lipofibromatosis),
PMF (primary myelofibrosis),
PSCN (pigmented spindle cell nevus of Reed),
SC (secretory carcinoma of the salivary gland),
SCT (spindle cell tumor of soft tissues),
SN (spitzoid neoplasms),
STAD (stomach adenocarcinoma).

Santoro M, et al. Genes 2020, 11, 424; doi:10.3390/genes11040424

RET ONCOGENIC CONVERSION IN HUMAN NEOPLASMS

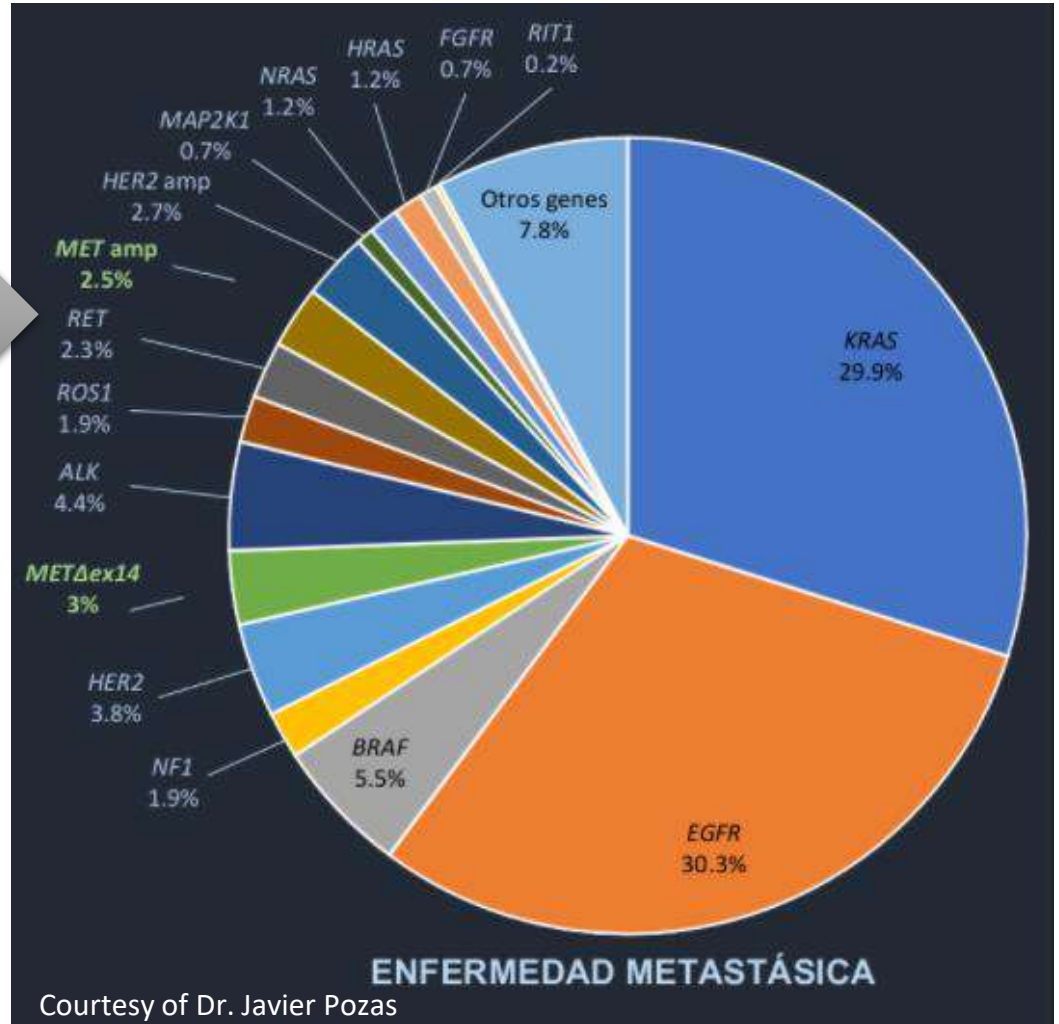


RET mutations in MTCs in up to 60% somatic/>95% germline:

- M918T = 70.5%
- C634R = 4.9%
- A993F = 2.2%
- C634Y = 2.1%
- C634W = 1.9%
- C630R = 1.5%
- E632_L633 del = 1.4%
- D999_E901 del = 1.4%
- C620R = 0.6%
- S991A = 0.6%

RET rearrangements occur in up to 10–20% of PTCs:

- CCDC6 = 59%
- NCOA4 = 36%



Courtesy of Dr. Javier Pozas

Skoulidis, F et al. Nat Rev Cancer. 2019; Subbiah V, et al. J Clin Oncol 2020; 38
Subbiah V & Cote GJ. Cancer Discov 2020;10:498–505,

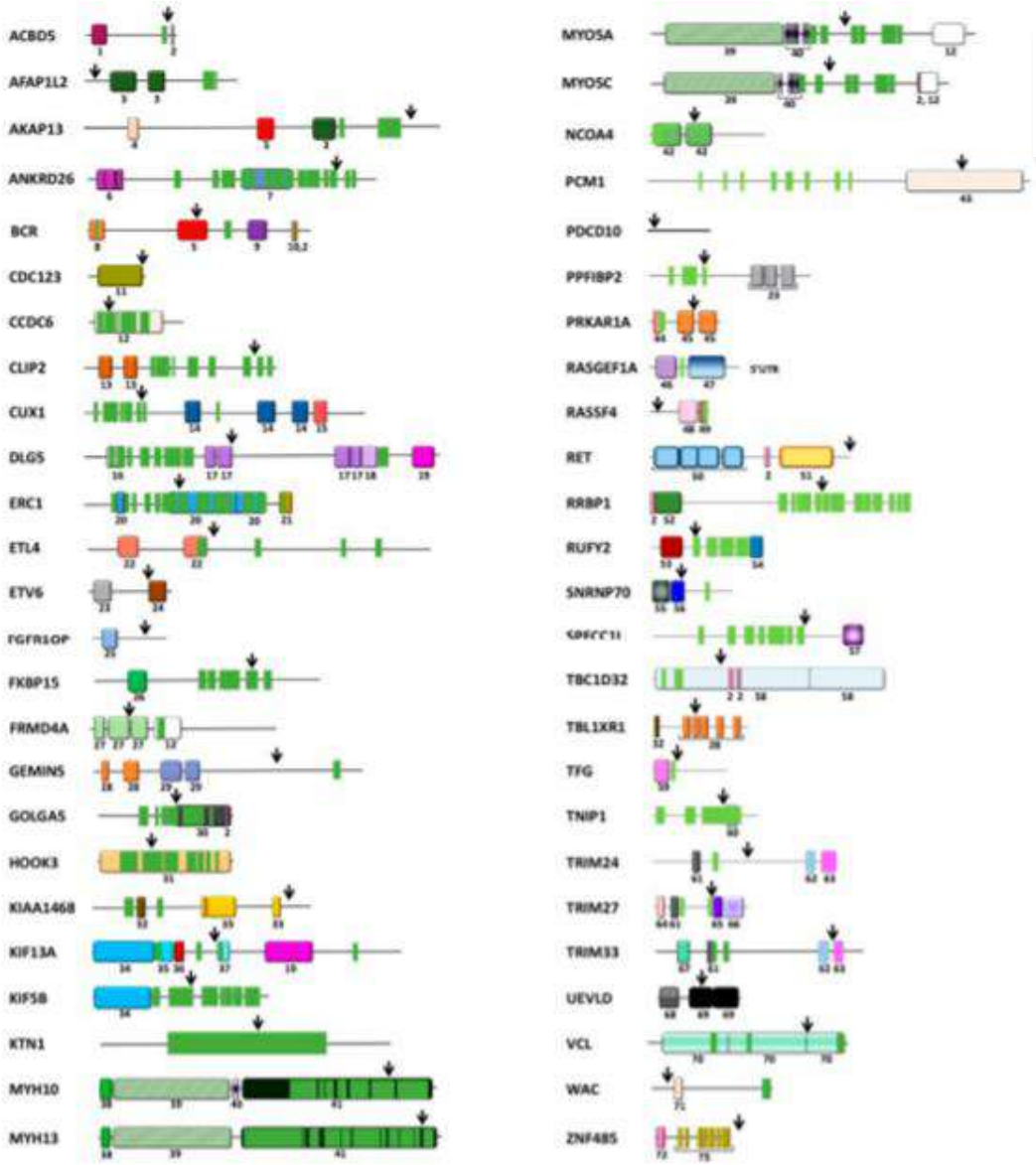
RET ONCOGENIC CONVERSION IN HUMAN NEOPLASMS

RET rearrangement in other tumors (0.7%):
breast (0.0%–0.21%), colon (0.0%–0.26%), oesophageal (0.0%–0.17%), ovarian (0.0%–0.17%), prostate (0.08%), stomach (0.81%) carcinoma, and acute myeloid leukaemia (0.0%–0.5%)

Somatic RET mutations in other tumors:
anaplastic thyroid carcinoma (4.3%), melanoma (6.6%), desmoplastic melanoma (20%), cutaneous squamous cell carcinoma (10%), colorectal cancer (3.6%-6.9%), paraganglioma, breast cancer and ureter urothelial carcinoma

Passenger mutations?

Skoulidis, F et al. Nat Rev Cancer. 2019; Subbiah V, et al. J Clin Oncol 202
Subbiah V & Cote GJ. Cancer Discov 2020;10:498–505,



RET ONCOGENIC CONVERSION IN HUMAN NEOPLASMS

Representation of RET fusion protein partners.

Arrows indicate the most frequent breakpoint sites in partner proteins.

Santoro M, et al. Genes 2020, 11, 424; doi:10.3390/genes11040424

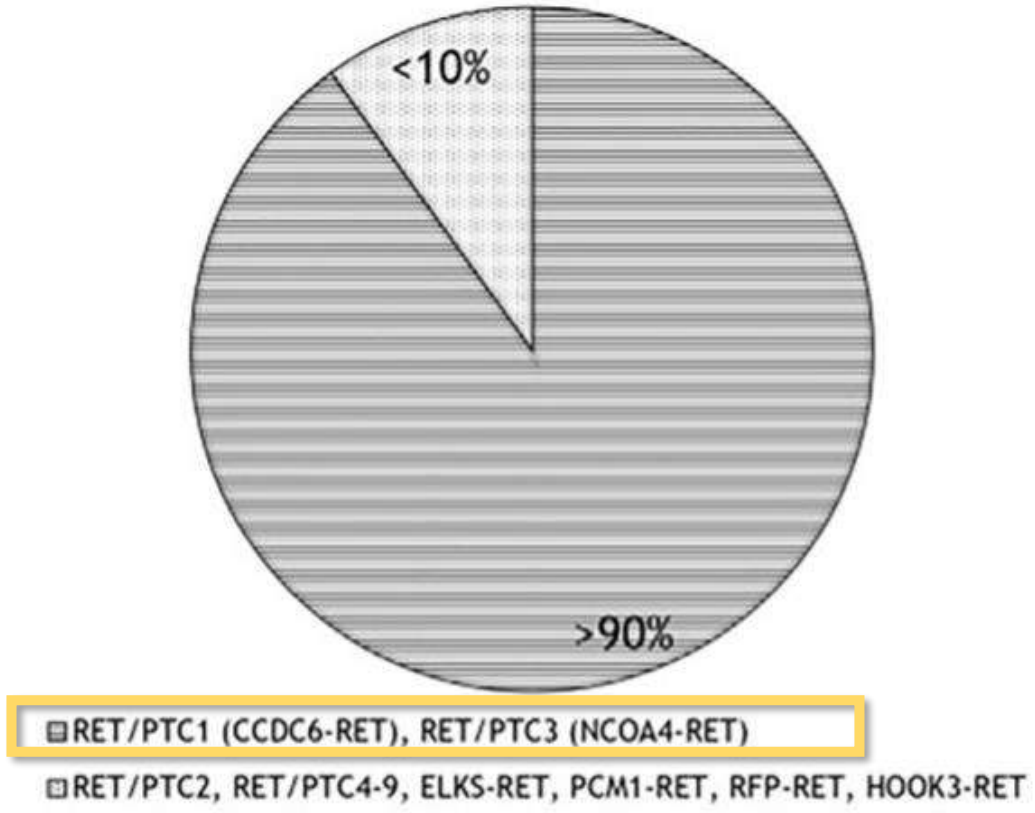
RET ONCOGENIC CONVERSION IN HUMAN NEOPLASMS

Most commonly, secondary to a breakpoint in RET intron 11, the RET coding sequence from exon 12 to the STOP codon is included in the fusion. However, in rare instances, the fusion product starts from RET alternative exons, such as exon 3, 7, 9 (EC portion), 10 (TM: transmembrane segment), or 11 (IC portion).

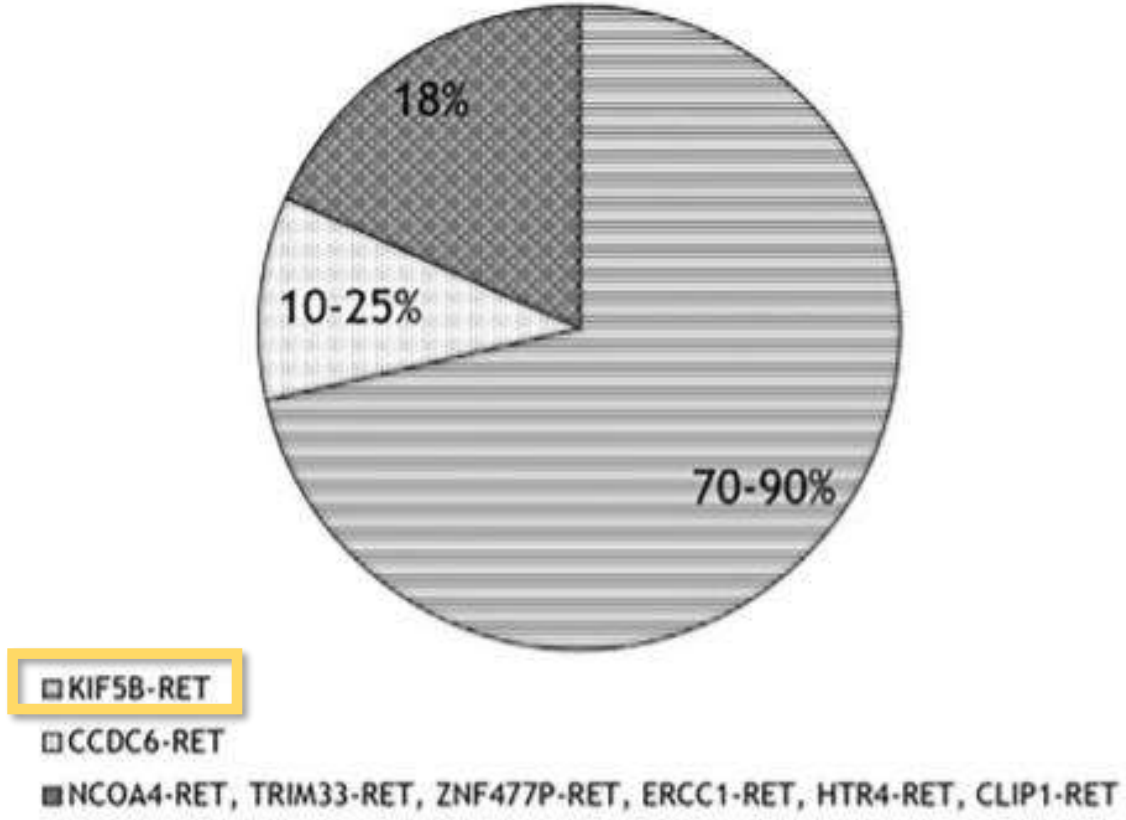
Santoro M, et al. Genes 2020, 11, 424; doi:10.3390/genes11040424

RET ONCOGENIC CONVERSION IN HUMAN NEOPLASMS

Papillary thyroid carcinoma

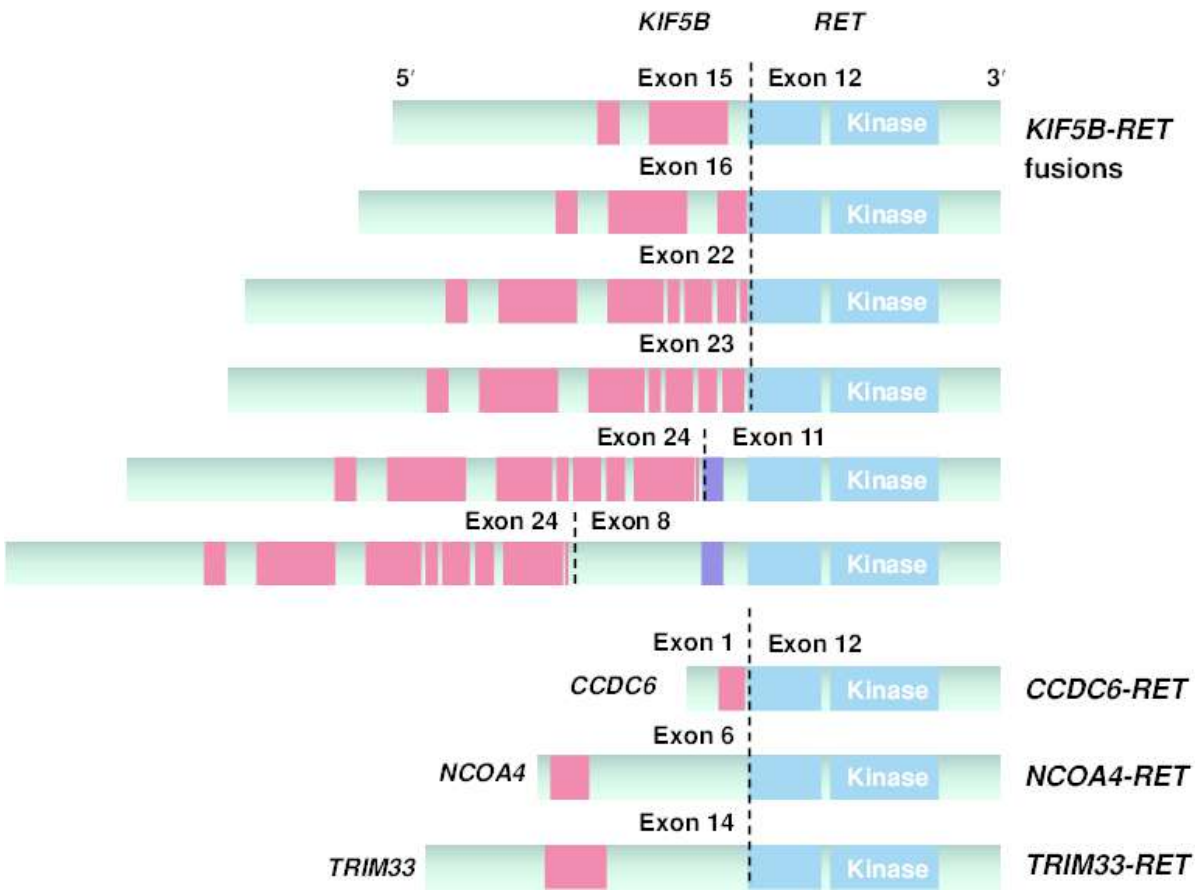


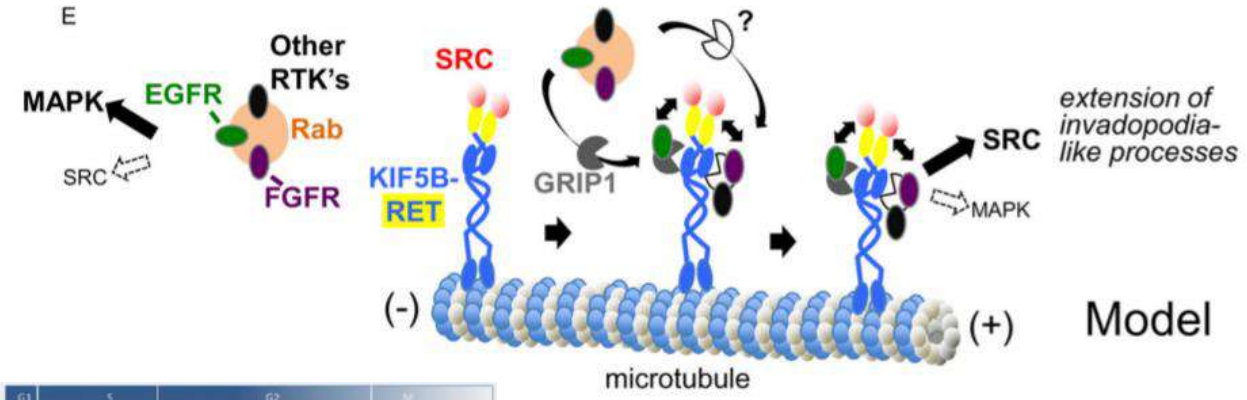
Lung carcinoma

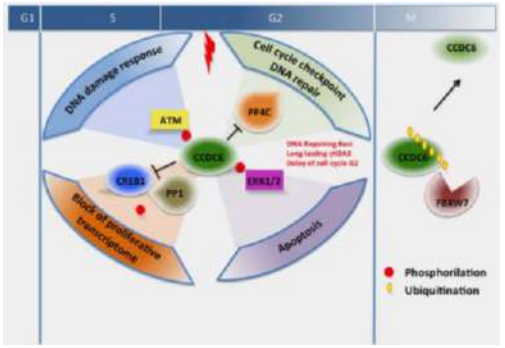


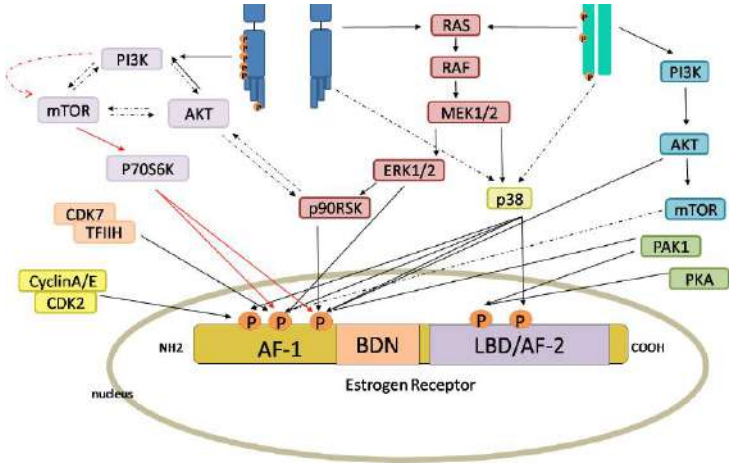
Li AY, et al. Cancer Treat Rev 2019; 81: 101911-101911

FUNCTIONAL CONSEQUENCES OF RET GENE FUSIONS



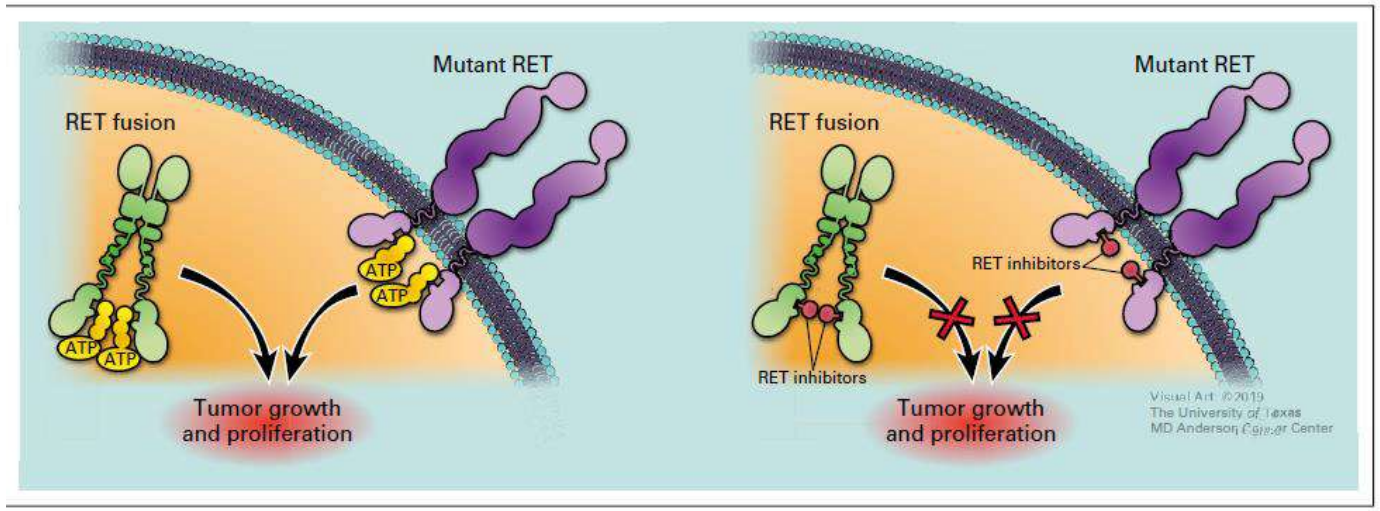




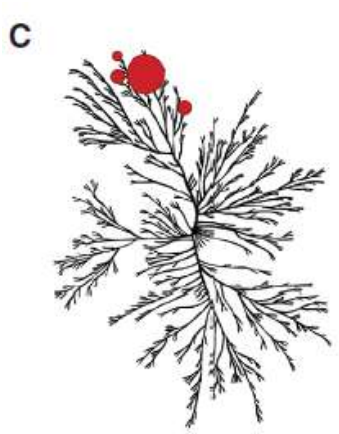


Li AY, et al. Cancer Treat Rev 2019; 81: 101911-101911

CLINICAL INVOLVEMENT …



SELPERCATINIB*
PRALSETINIB**



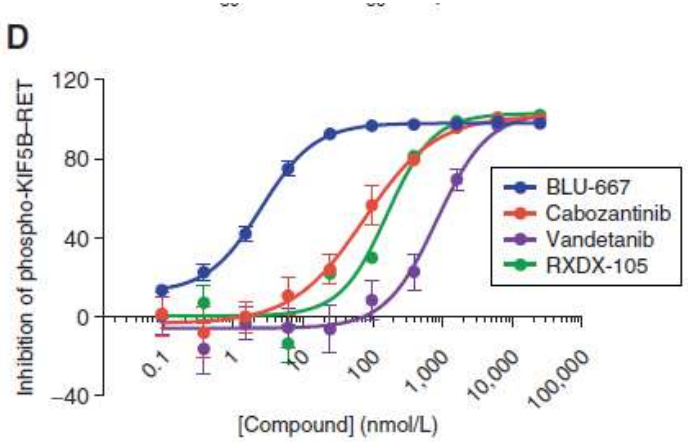
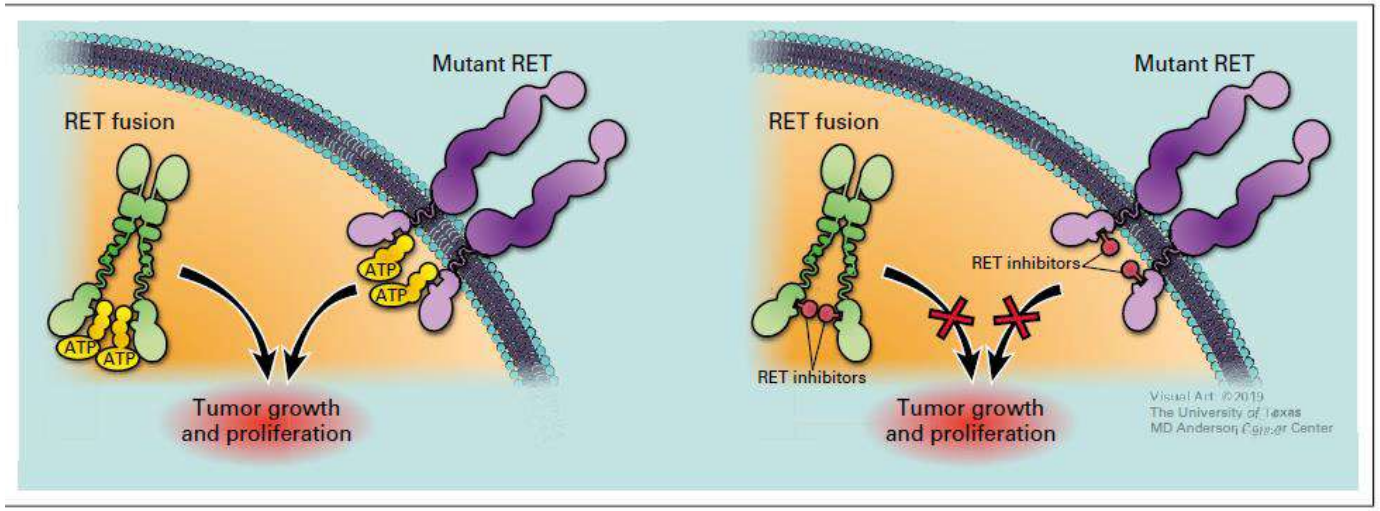


Table 1. Biochemical potency of BLU-667 and MKIs against activated RET mutants and fusion variants

	Biochemical IC_{50}, nmol/L					
Compound	WT RET	RET V804L	RET V804M	RET M918T	CCDC6-RET	VEGFR2
BLU-667	0.4	0.3	0.4	0.4	0.4	35
Cabozantinib	11	45	162	8	34	2
Vandetanib	4	3,597	726	7	20	4
RXDX-105	3	188	102	4	7	17

Subbiah V, et al. Cancer Discovery 2018

CLINICAL INVOLVEMENT …



SELPERCATINIB*
PRALSETINIB**

Thyroid

*FDA approval (May 2020) for adult and pediatric patients ≥ 12 years of age with advanced or metastatic RET-mutant MTC or RET-fusion RAI-DTC who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). EMA approval (Feb 2021) advanced thyroid cancer in adults who had previously been treated with the cancer medicines sorafenib or lenvatinib or both; advanced medullary thyroid cancer in patients aged from 12 years who had previously been treated with the cancer medicines cabozantinib or vandetanib or both. EMA approval (Dec 2020) CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product selpercatinib, intended for the treatment of cancers that display rearranged during transfection (RET) gene alterations: RET-fusion positive non-small cell lung cancer (NSCLC), RET-fusion positive thyroid cancer and RET-mutan t medullary-thyroid cancer (MTC).

**FDA approval (Dec 2020) for adult and pediatric patients ≥ 12 years of age with advanced or metastatic RET-mutant MTC or RET-fusion RAI-DTC who require systemic therapy and are and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Lung

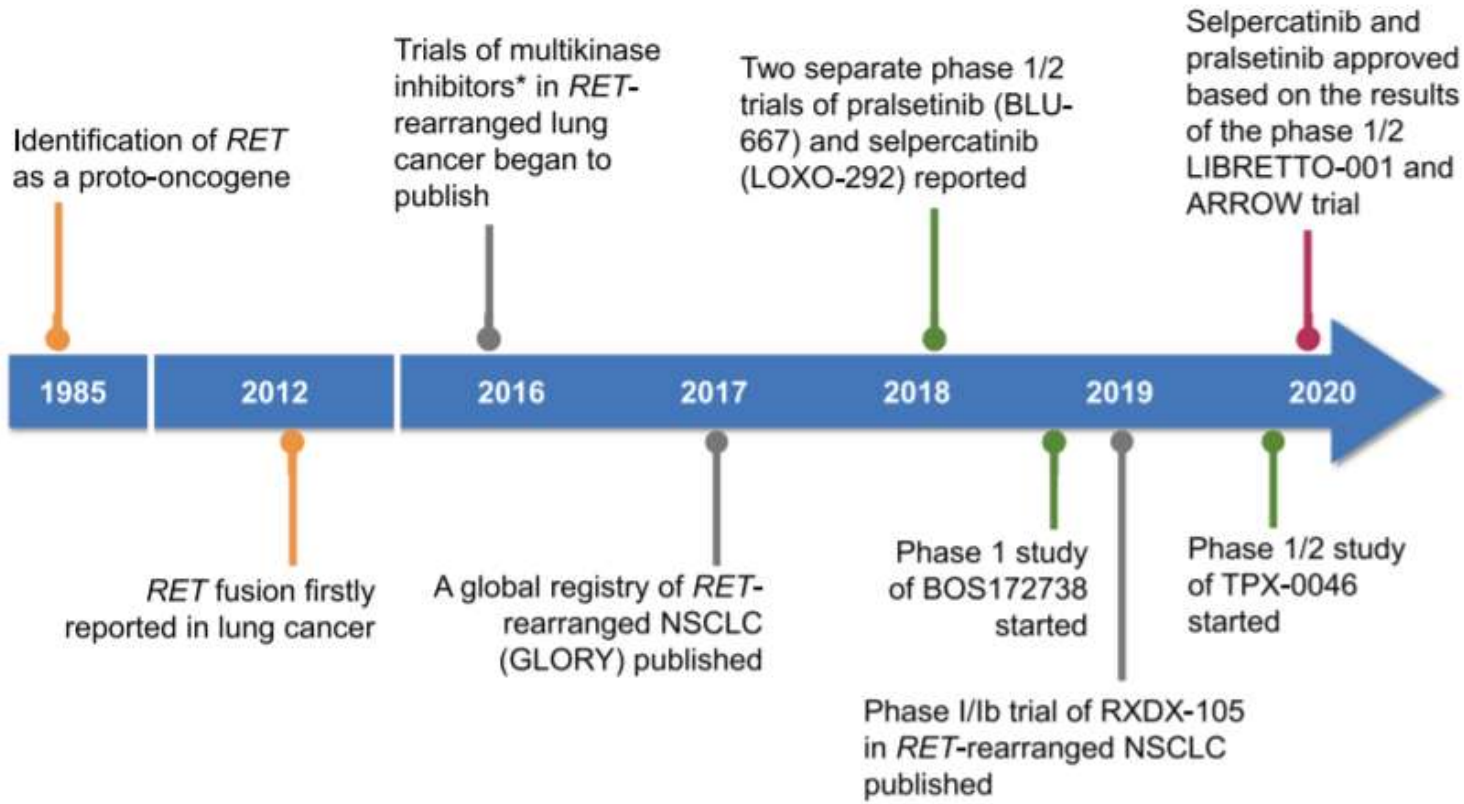
*FDA approval (May 2020) for adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC). EMA approval (Apr 2021) for advanced non-small cell lung cancer in adults who had previously received immunotherapy or platinum-based cancer medicines or both

** FDA approval (Sep 2020) for adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.:

Subbiah V, et al. J Clin Oncol 2020; 38

CLINICAL INVOLVEMENT …

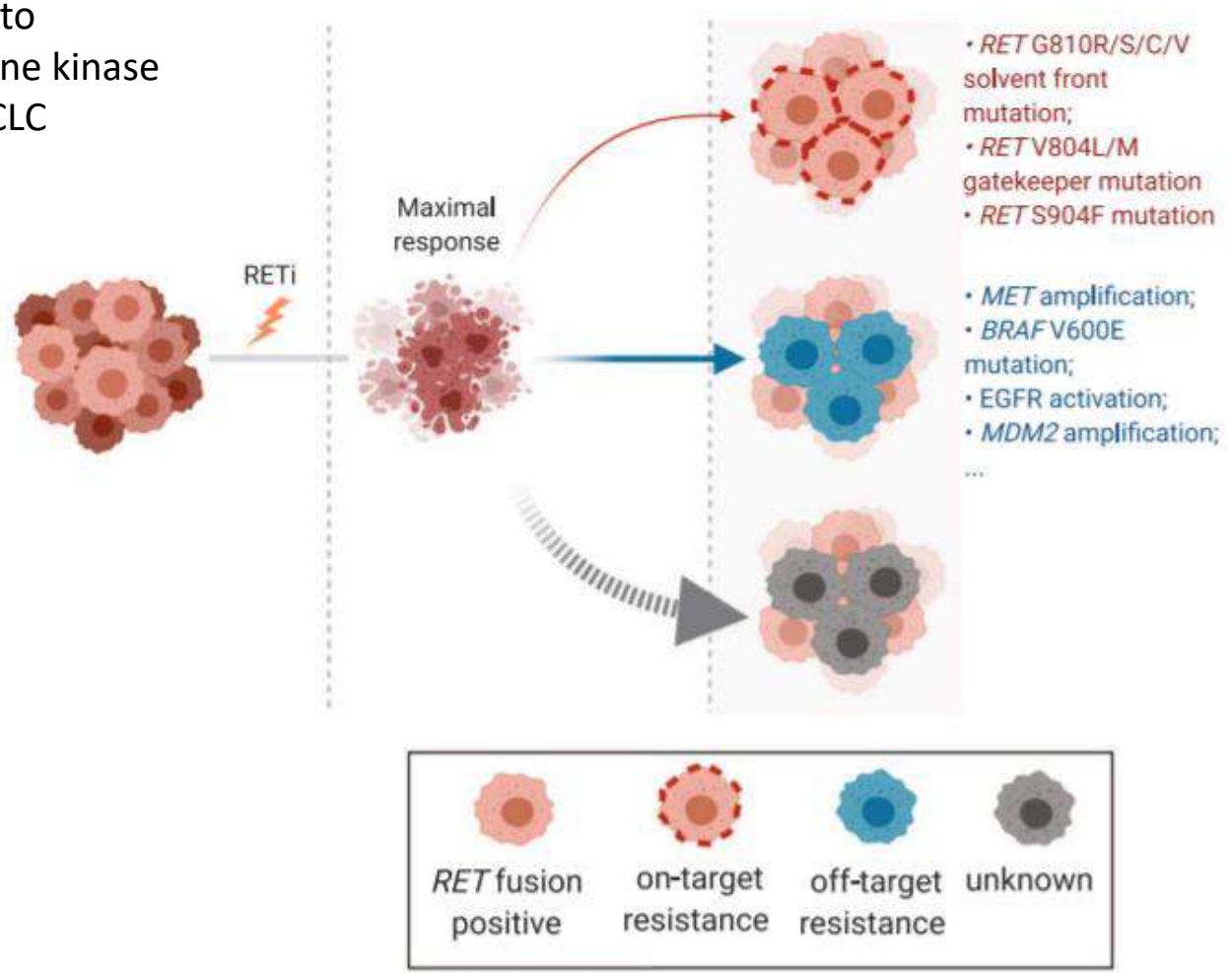
Milestones in the discovery and clinical studies of RET fusion-positive/RET-mutant



Lu Ch. Cancer Treat Rev 2021; 96: 102153

MECHANISMS OF ACQUIRED RESISTANCE

Mechanisms of acquired resistance to multikinase and selective RET tyrosine kinase inhibitors in RET fusion-positive NSCLC



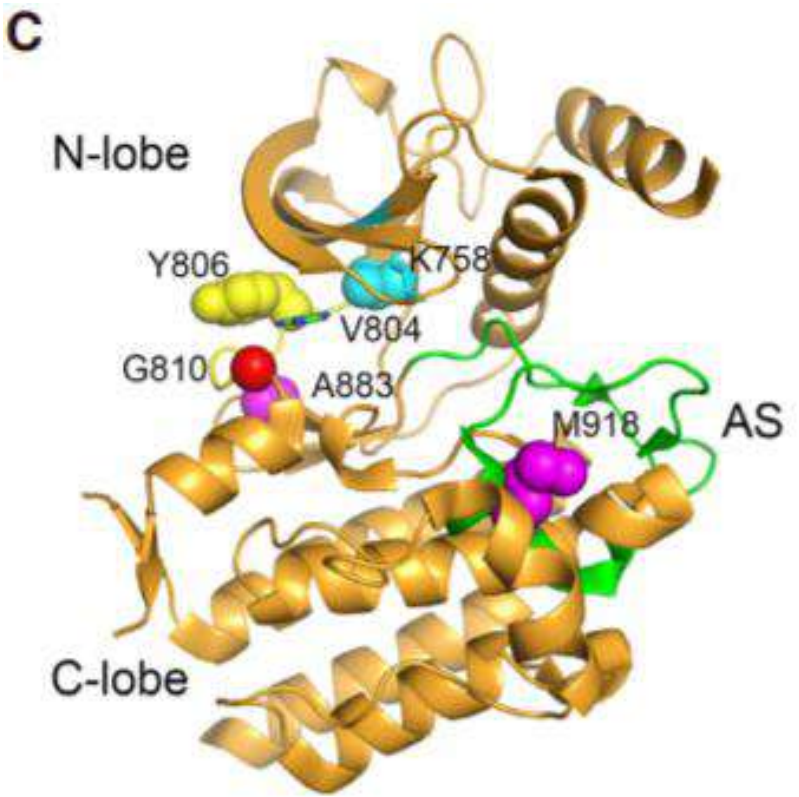
Lu Ch. Cancer Treat Rev 2021; 96: 102153

MECHANISMS OF ACQUIRED RESISTANCE

Mechanisms of acquired resistance to multikinase and selective RET tyrosine kinase inhibitors in RET mutant MTC

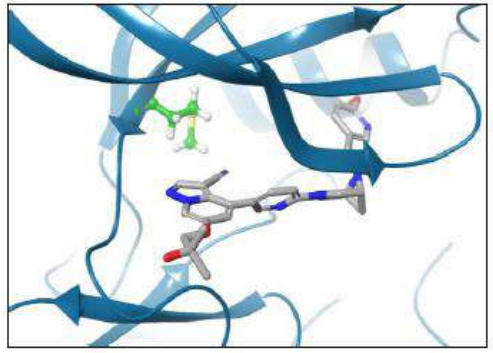
Identification of selpercatinib-resistant RET mutants and cross-profiling with pralsetinib

Method	Mutant	Selecting selpercatinib concentration (nM)		Mutant clone count	IC_{50} (nM) (fold: mutant/wt)	
		150	300		Selpercatinib	Pralsetinib
Isolation from mutation library	V738A	2	0	2	238.8 ± 7.2 (29)	177.5 ± 6.7 (19)
	Y806C	1	0	1	174.4 ± 5.4 (21)	295.8 ± 10.7 (32)
	Y806N	2	0	2	149.8 ± 6.3 (18)	292.5 ± 5.9 (32)
	G810S	20	11	31	880.2 ± 25.6 (107)	390.6 ± 10.8 (42)
Cell culture with selpercatinib	G810S	120		2	880.2 ± 25.6 (107)	390.6 ± 10.8 (42)
	G810C	120		1	1227 ± 44.1 (150)	641.7 ± 19.1 (70)
N/A	G810R	N/A		N/A	2744 ± 160.6 (334)	2650 ± 287.3 (288)
	V804L	N/A		N/A	17.2 ± 0.5 (2)	1.8 ± 0.6 (2)
	V804M	N/A		N/A	55.9 ± 1.6 (7)	16.8 ± 0.8 (2)
	wt	N/A		N/A	8.2 ± 0.4 (1)	9.2 ± 0.4 (1)

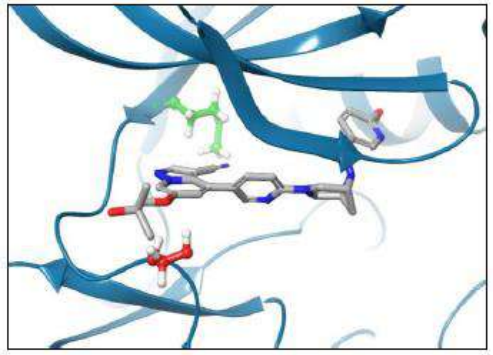


Liu et al. Cancer Drug Resist 2020;3:472-81

MECHANISMS OF ACQUIRED RESISTANCE



Crystal structure of selpercatinib (gray) bound to RET V804M (V804M gatekeeper residue shown in green). Selpercatinib is a potent inhibitor of RET V804M.



Model of G810S solvent front mutation (in red) shows Ser810 close to the space where selpercatinib binds, consistent with a potency loss in KIF5B-RET G810S+V804M.

	Selpercatinib IC_{50} (nM)	Pralsetinib IC_{50} (nM)
Founder alterations		
CCDC6-RET	10	5
KIF5B-RET	3	3
RET M918T	9	1
Acquired resistance mutations		
KIF5B-RET G810S	53	81
KIF5B-RET V804L	5	2
KIF5B-RET V804M	7	10
KIF5B-RET G810S+V804M	434	370
RET M918T+G810S	39	141

	LOX-18228 IC_{50} (nM)	LOX-19260 IC_{50} (nM)
Founder alterations		
CCDC6-RET	4	4
KIF5B-RET	1	1
RET M918T	4	6
Acquired resistance mutations		
KIF5B-RET G810S	8	11
KIF5B-RET V804L	56	21
KIF5B-RET V804M	71	34
KIF5B-RET G810S+V804M	35	36
RET M918T+G810S	6	8

Kolakowski GR, et al. Presented at AACR 2021

CONCLUSIONS

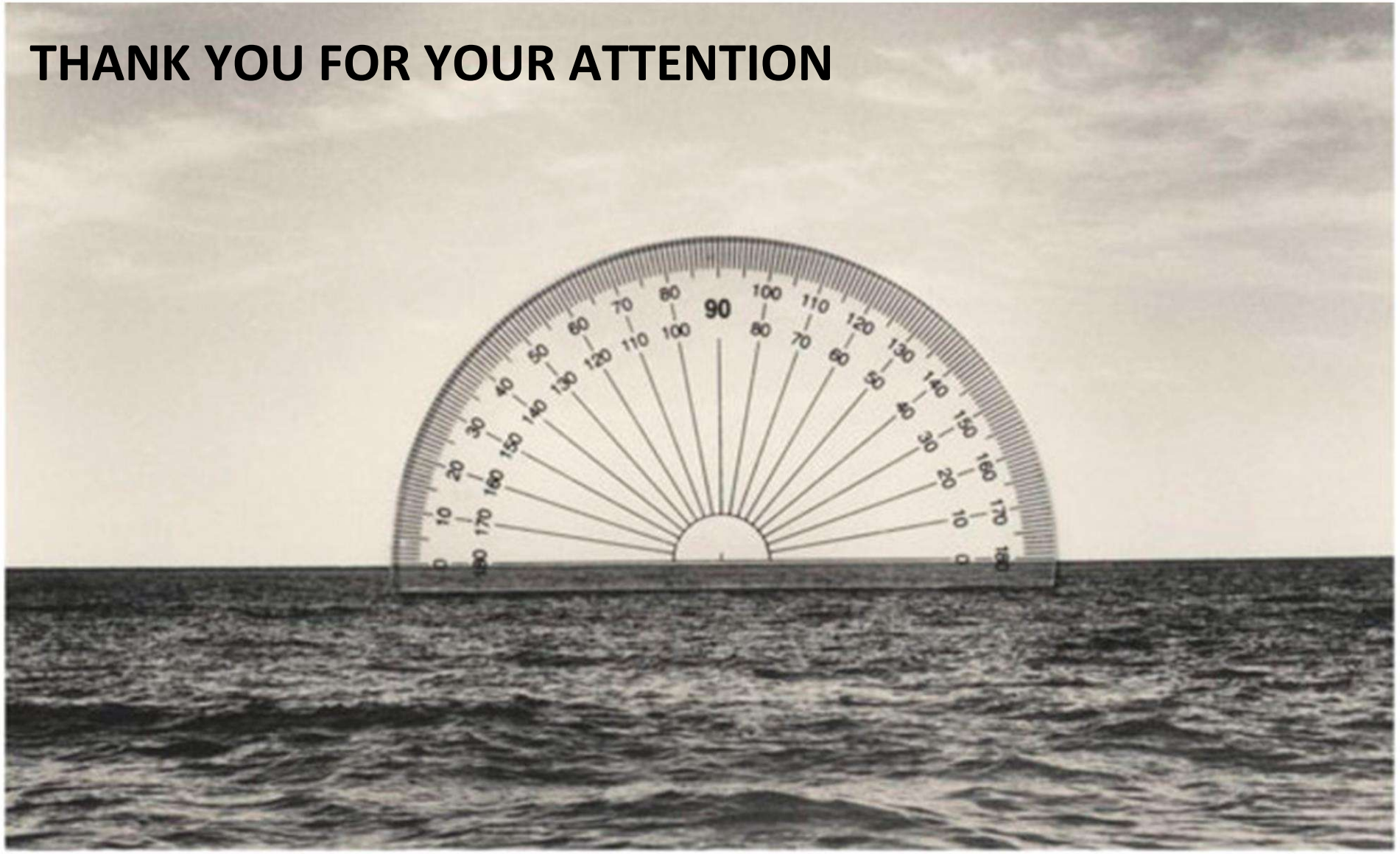
Biological knowledge on Advanced solid tumors has rapidly increase in last years.

This molecular knowledge has led the identification of potential therapeutic targets that are now at patients´ disposal, such as RET genomic alterations and RET inhibitors.

At this point, we need to improve the availability of molecular testing and access to specific therapeutic treatments and clinical trials: genetic counseling and treatment implications.

Research on additional targets and potential mechanisms of primary and acquired resistance are needed to improve the therapeutic algorithm and consider sequence vs combination therapies.

The multidisciplinary team is key to achieve all those present and future challenges.


THANK YOU FOR YOUR ATTENTION