Challenges in first line and subsequent treatments for patients with and without RET mutations MTC: Are new options on the Horizon?



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DISCLOSURES

Dr. Alonso Gordoa financial interests:

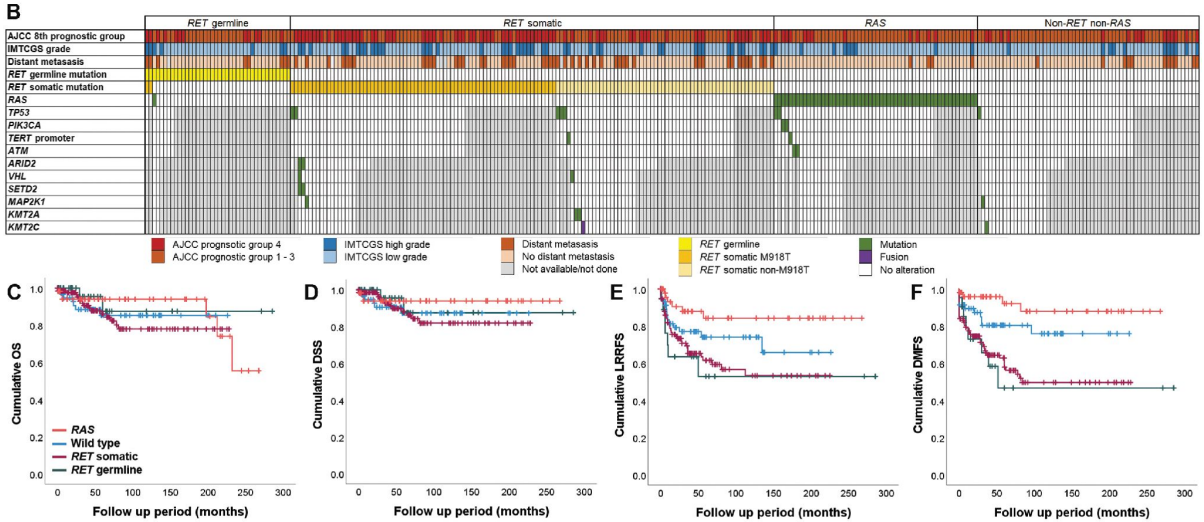
- Personal conflicts of interest Scientific consultancy role (speaker and advisory roles) from Lilly, Ipsen, Astellas, Bayer, Johnson & Johnson, Eisai, Novartis, MSD, Recordati, Pfizer, Esteve, BMS.

- Research support Research grants from IPSEN, Johnson & Johnson.

RET MUTATION STATUS & NGS AVAILABILITY

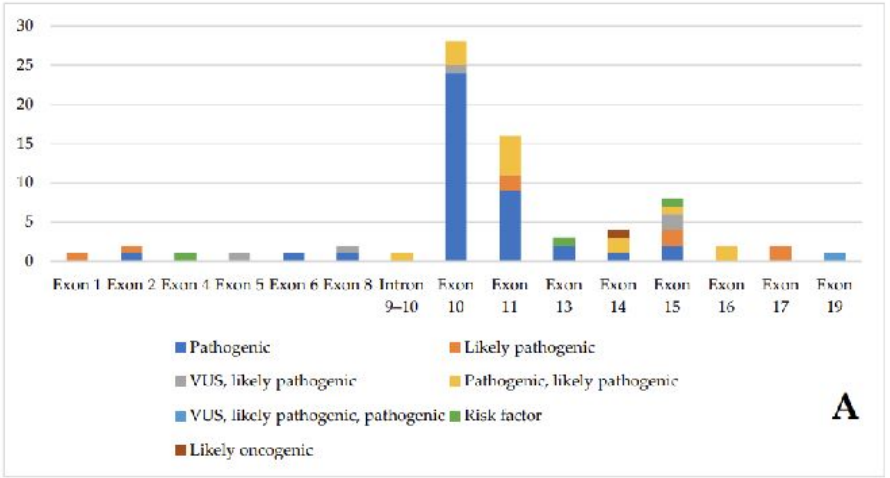
	All cases (N = 290)	RET *germ line mutations* (n = 40)[a]	RET *somatic mutations* (n = 133)[a]	RAS *somatic mutations* (n = 56)[a]	RET/RAS *WT* (n = 61)
Male:female ratio	138:152 (1:1.1)	18:22 (1:1.2)	77:56 (1:0.7)	18:38 (1:2.1)	35:36 (1:1.4)
Age, years	57 (7–88)	42 (7–66)	59 (22–88)	57 (7–79)	58 (25–84)
Tumor size, cm	2.0 (0.1–11.0)	1.2 (0.1–6.0)	2.1 (0.4–8.0)	2.0 (0.3–11.0)	1.9 (0.3–6.0)
AJCC eighth edition overall stage					
I	92 (31.7)	13 (32.5)	29 (21.3)	24 (42.9)	26 (42.6)
II	43 (14.8)	4 (10.0)	13 (9.6)	12 (21.4)	14 (23.0)
III	41 (14.1)	11 (27.5)	17 (12.5)	7 (12.5)	6 (9.8)
IV	114 (39.3)	12 (30.0)	77 (56.6)	13 (23.2)	15 (24.6)

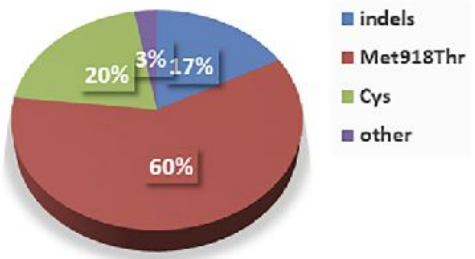
NGS confirmed sMTC
73% RET
18% RAS
9% No RET/No RAS
* Other recurrent alterations: TP53 (4.2%), ARID2 (2.9%), SETD2 (2.9%), KMT2A (2.9%), and KMT2C (2.9%).

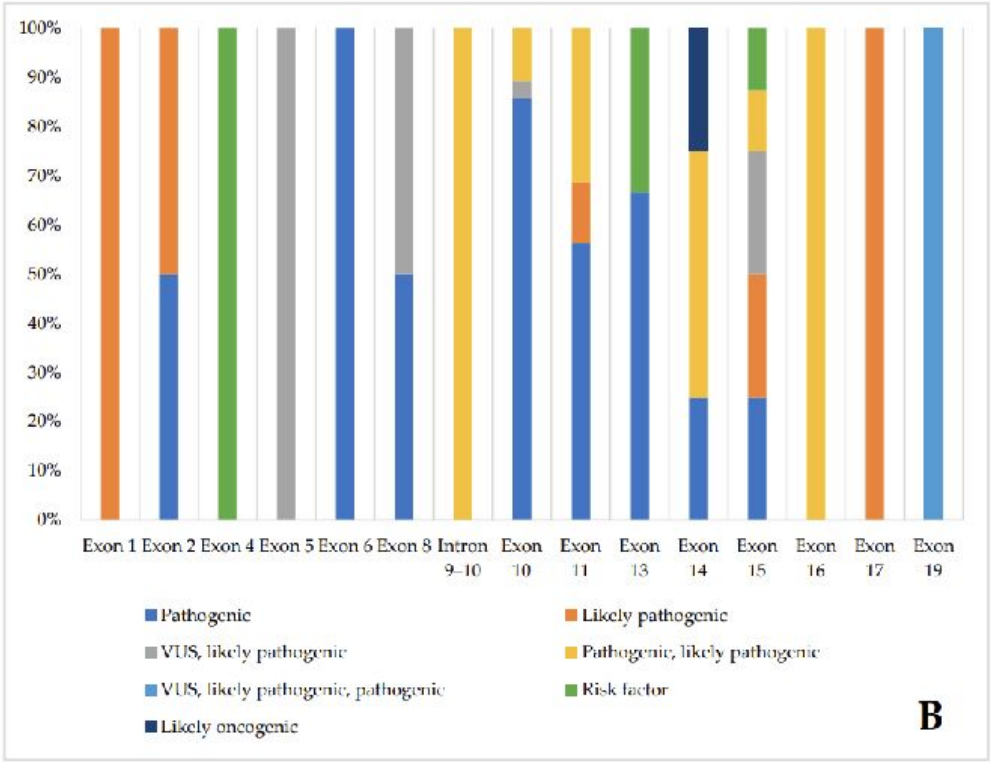


Parimi V, et al. J Precision Oncology (2023) 7:10; Desilets A, et al. Cancers 2023, 15(16), 4146; Rosella E, et al. Endocrine. 2023 Aug;81(2):206-215; Shirali AS, et al. J Endocr Soc. 2024 Apr 24;8(6):bvae048; Xu B, et al. Thyroid. 2024 Feb;34(2):167-176.

RET MUTATION STATUS & NGS AVAILABILITY

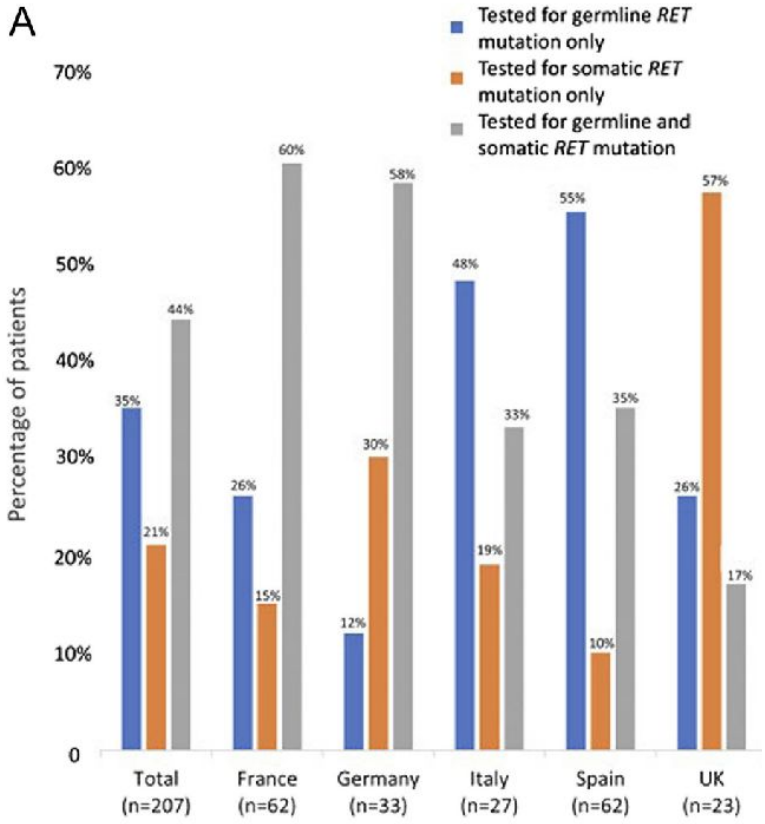






Tenore CR, et al. Genes (Basel). 2025 Dec 9;16(12):1472; Elisei R, et al. J Clin Endocrinol Metab. 2022 Jul 14;107(8):2195-2202..

RET MUTATION STATUS & NGS AVAILABILITY



Overall, 75% were tested for RET mutation (35% germline only, 21% somatic only, 44% both)

Common physician-cited barriers to RET mutation testing included high cost, difficulty accessing latest tests, and time delay for results.

Segall G, et al. Eur Thyroid J. 2024 Feb 19;13(1):e230172.

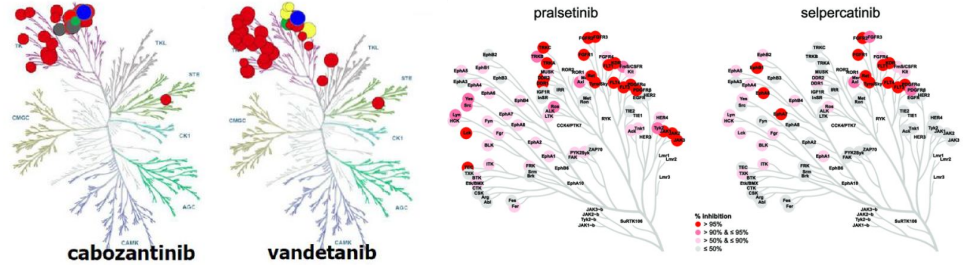
THE RELEVANCE OF RET MUTATION STATUS INFORMATION

- WHY IS SO IMPORTANT TO HAVE THIS INFORMATION?

GENETIC COUNSELING



FUP & TREATMENT IMPLICATION

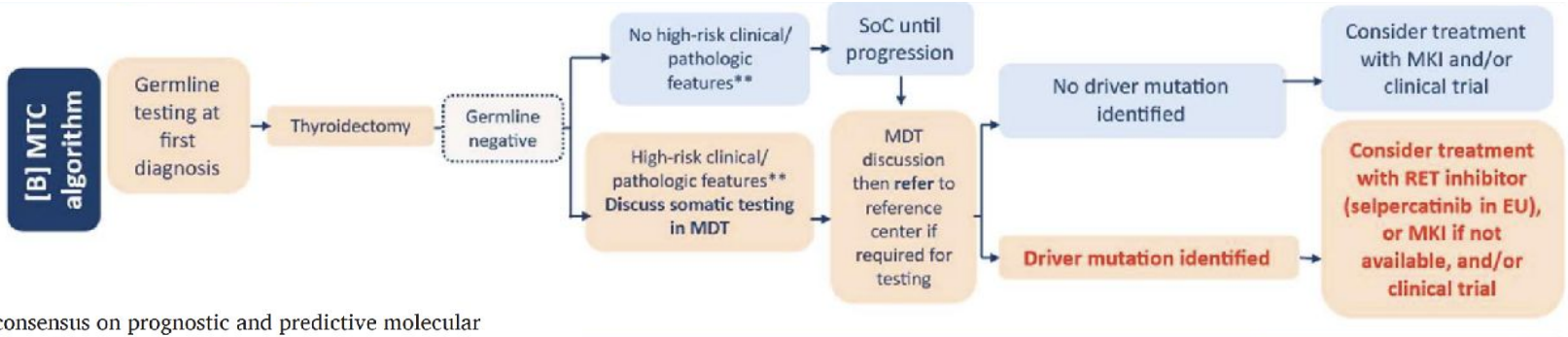


IC50, nM	RET WT	RET M918T	RET V804M	VEGFR2
Vandetanib	4	7	726	4
Cabozantinib	11	8	162	<1
Pralsetinib	0.4	0.4	0.4	35
Selpercatinib	0.4	0.7	0.8	100

Shehata M, et al. J Adv Res. 2023 Mar:45:87-100; Gauduchon T, et al. Future Oncol. 2025 Aug;21(20):2585-2592.

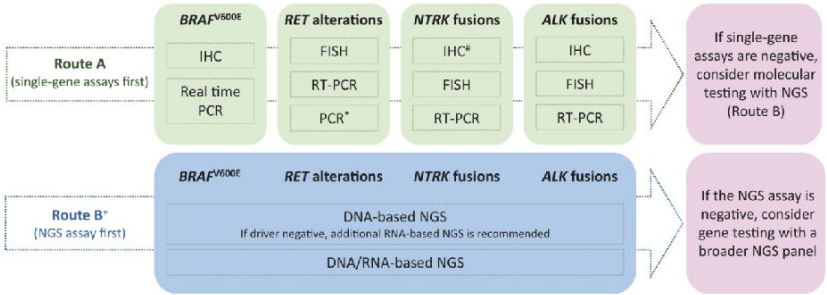
THE RELEVANCE OF RET MUTATION STATUS INFORMATION

- WHY IS SO IMPORTANT TO HAVE THIS INFORMATION?



SEAP-GETNE consensus on prognostic and predictive molecular biomarkers in thyroid cancer

	Turnaround time	Input material	Precise annotation of variants	Analytical sensitivity	Diagnostic sensitivity
BRAF V600E and *RET* mutations					
Sanger sequencing	1–2 weeks	High (6–8 slides)	Yes	Low	High
IHC[a]	Hours	Low (1 slide)	Yes	High	Low
Real time PCR	2–3 days	Intermediate (3–5 slides)	Sometimes	High	Intermediate
DNA-based NGS	Variable (2–3 days for some amplicon assays)	Variable (low for some amplicon assays)	Yes	High	High



Ryska A, et al. Eur Thyroid J. 2025 Jul 7;14(4):e250024.
Ruz Caracuel I, et al. Rev Esp Patol. 2026 Apr-Jun;59(2):100859.

FIRST LINE TREATMENT IN PATIENTS RET+ MTC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Selpercatinib in Advanced *RET*-Mutant Medullary Thyroid Cancer

Key Eligibility Criteria
- Unresectable locally advanced or metastatic *RET*-mutant MTC
- No prior history of treatment with kinase inhibitors
- Documented RECIST 1.1 PD within 14 months (centrally reviewed)
- *RET* mutation identified via NGS or PCR

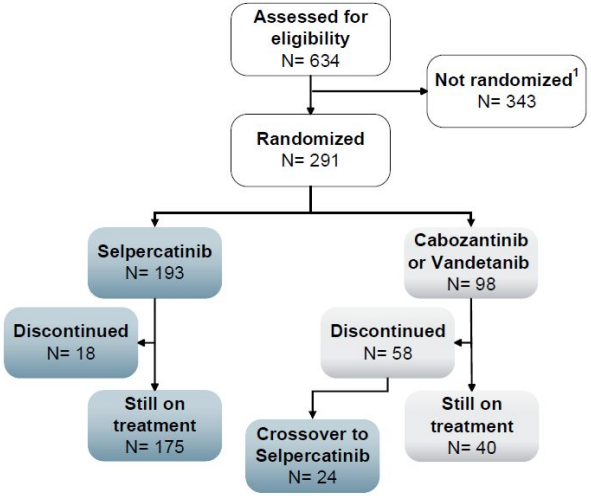
Stratification factors
- Mutation status: (M918T vs other)
- Physician's choice of treatment if randomized to control arm, with declared intent before randomization

R 2:1

Selpercatinib (160 mg BID)
N= 193

Physician's choice of **Cabozantinib** (140 mg QD) or **Vandetanib** (300 mg QD)
N= 98

Optional Crossover → **Selpercatinib** (Upon BICR confirmed PD)



Primary endpoint: PFS per RECIST 1.1 by BICR

Secondary endpoints:
- **Efficacy** (TFFS[1] by BICR and investigator, PFS by investigator, ORR by BICR and investigator, and OS)
- **Safety**

[1] TFFS was tested conditionally on achieving statistical significance for PFS, adjusted for multiplicity and tested against a two-sided significance level of 0.05

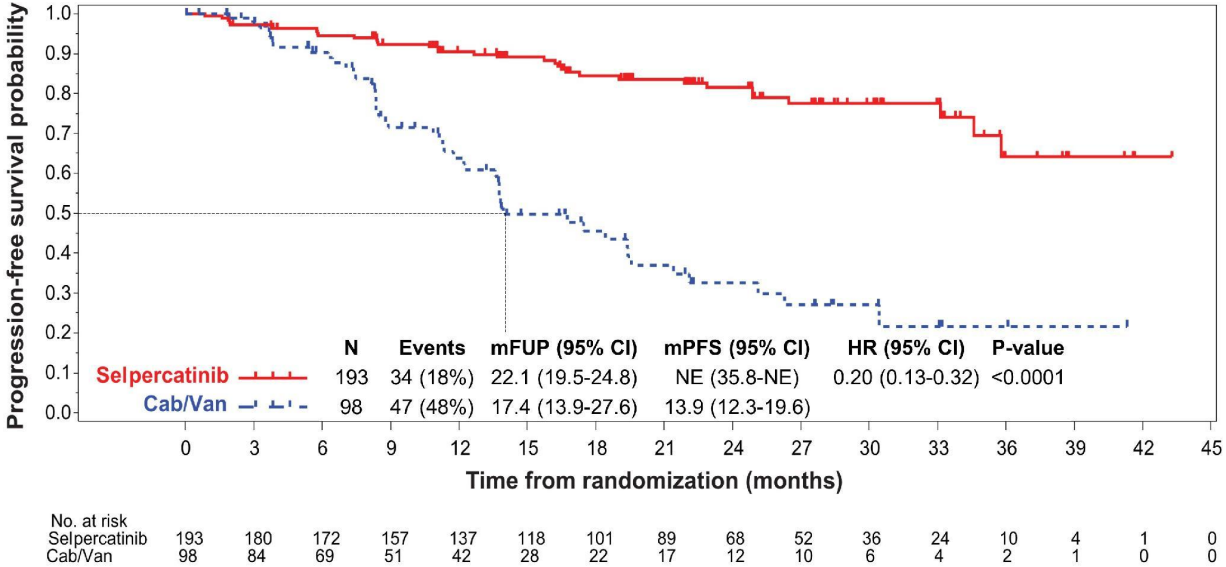
BICR, blinded Independent Central Review; NGS, next-generation sequencing; PCR, polymerase chain reaction; PFS, progression-free survival; TFFS, treatment failure-free survival; ORR, overall response rate; OS, overall survival, PD, progressive disease

Hadoux J, et al. N Engl J Med. 2023 Oct 21. doi: 10.1056/NEJMoa2309719.
Hadoux J, et al Presented at ESMO 2023

FIRST LINE TREATMENT IN PATIENTS RET+ MTC

PROGRESSION FREE SURVIVAL

mFUP = 25 months



Kaplan-Meier plot for progression-free survival as assessed by BICR. mFUP and mPFS are reported in months. PFS estimates at 24-months were 81.5% (95% CI 74.0-87.0) for selpercatinib and 32.5% (95% CI 20.6-44.9) for control; P≤0.0001. Investigator-assessed PFS was similar with HR of 0.158 (95% CI 0.100-0.250); P<0.0001. Abbreviations: Cab/Van, Cabozantinib/Vandetanib; mFUP, median follow-up time; mPFS median progression-free survival: HR, hazard ratio; NE, not estimable.

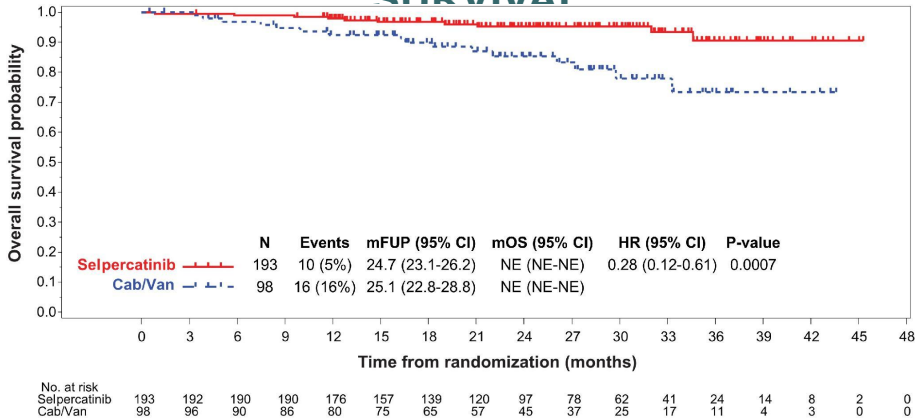
Wirth L, et al. Presented at ATA 2024

FIRST LINE TREATMENT IN PATIENTS RET+ MTC

ORR

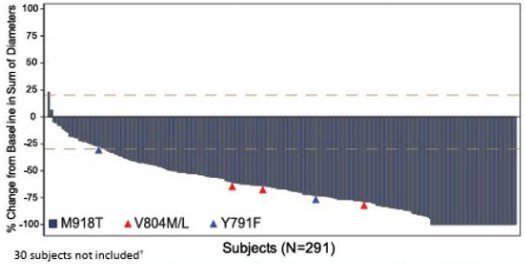
	Selpercatinib (N=193) n (%) [95% CI]	Cab/Van (N=98) n (%) [95% CI]	HR or OR (95% CI)
ORR, n (%) [95% CI]	159 (82) [76-88]	43 (44) [34-54]	OR, 6.0 (3.5-10.4); P<0.0001
CR	37 (19) [14-25]	6 (6) [2-13]	
PR	122 (63) [56-70]	37 (38) (28-48)	
SD	23 (12) [8-17]	46 (47) [37-57]	
PD	4 (2) [0.6-5]	2 (2) [0.3-7]	
Not evaluable	7 (4) [2-7]	7 (7) [3-14]	
mDOR (95%CI) – months	NE (34.1-NE)	16.5 (10.4-19.6)	HR, 0.14 (0.08-0.26); P≤0.0001
mFUP† (95%CI) – months	18.3 (15.7-20.3)	20.4 (12.9, 24.0)	

OVERALL SURVIVAL



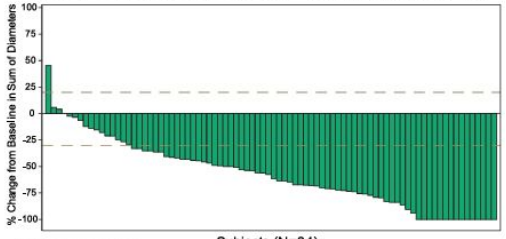
FIRST LINE TREATMENT IN PATIENTS RET+ MTC

M918T (TK domain)



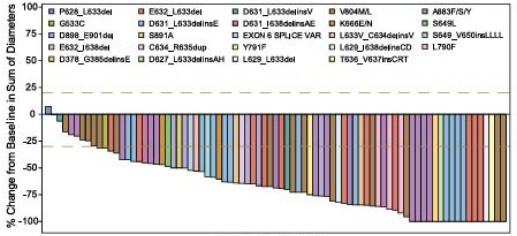
30 subjects not included†

Extracellular cysteine (dimerization)



16 subjects not included†

Other



7 subjects not included†

Tumor size reduction and specific pathogenic variants in LIBRETTO-001

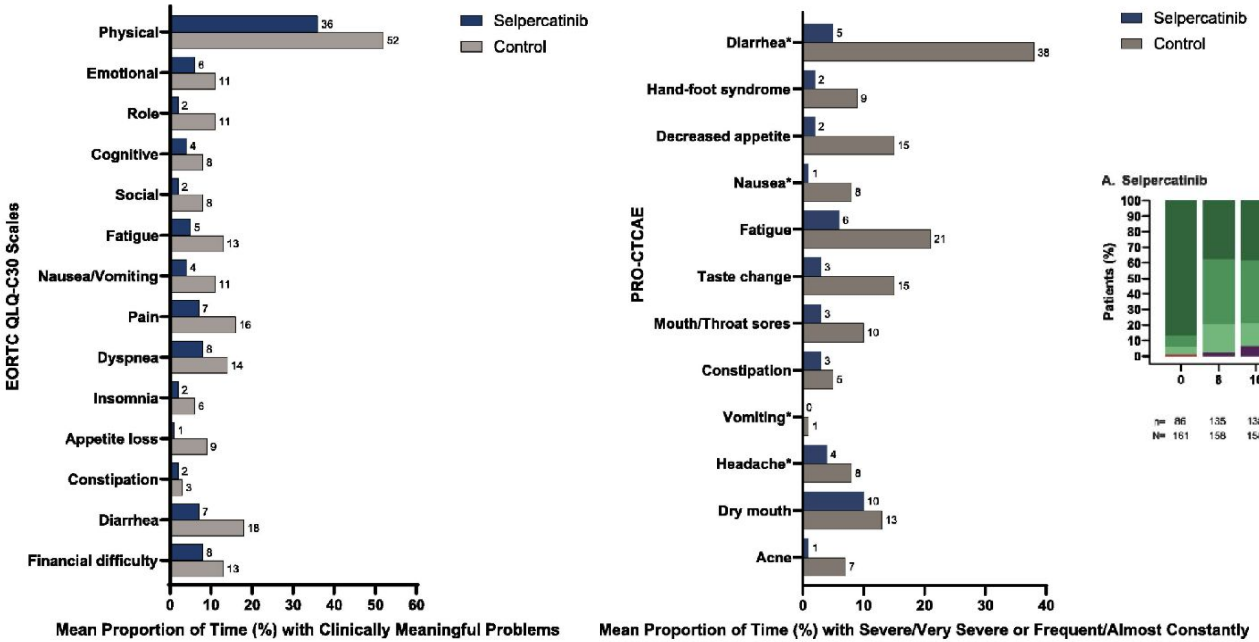
	NAÏVE n=79						TREATED n=48						TOTAL n=127					
	30%		80%		100%		30%		80%		100%		30%		80%		100%	
	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)
M918T	0.159	39/45 (87)	0.246	11/45 (24)	0.692	5/45 (11)	0.160*	20/28 (71)	0.737	8/28 (29)	0.385	4/28 (14)	1	59/73 (81)	0.188	19/73 (26)	0.234	9/73 (12)
V804	0.239*	3/5 (60)	1	1/5 (20)	1	0/5 (0)	1	4/5 (80)	1	1/5 (20)	1	0/5 (0)	0.412	7/10 (70)	1	2/10 (20)	0.596	0/10 (0)
EC	0.094^	12/18 (67)	0.499	2/18 (11)	1	1/18 (6)	0.320	6/6 (100)	1	1/6 (17)	1	0/6 (0)	0.568	18/24 (75)	0.405	3/24 (13)	0.461	1/24 (4)
OTHER MUTATIONS	0.680	10/11 (91)	0.680	1/11 (9)	1	1/11 (9)	0.661	8/9 (89)	1	2/9 (22)	1	1/9 (11)	0.360	18/20 (90)	0.563	3/20 (15)	1	2/20 (10)
TREATED PATIENTS													0.821	38/48 (79)	0.504	12/48 (25)	0.764	5/48 (10)

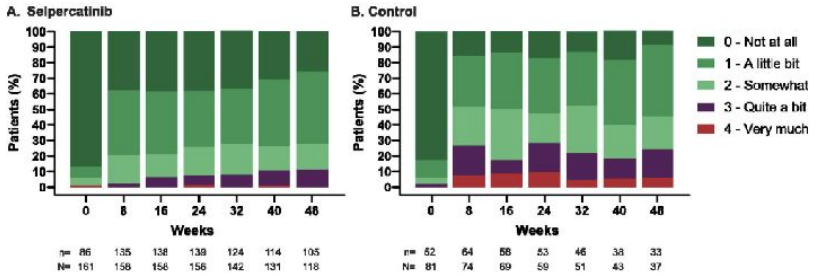
significant association | tendency | weak trend | no trends

Hadoux J, et al. Presented at ATA 2024
Gil Bernabé S, et al. Am J Med Genet C Semin Med Genet. 2025 Sep;199(3):228-238.

FIRST LINE TREATMENT IN PATIENTS RET+ MTC

Patient-Reported Tolerability





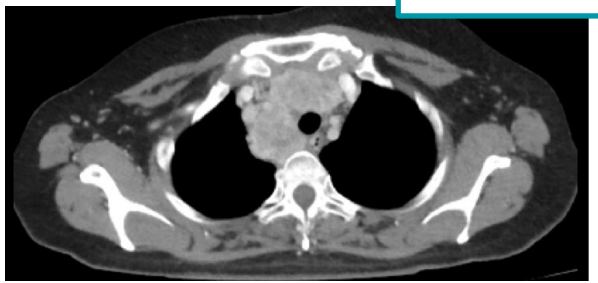
Patient-reported outcomes on GP5 "I am bothered by side effects of treatment" in (A) the selpercatinib group and in (B) the control group.

Rossella E, et al. Thyroid. 2025 Oct;35(10):1162-1172.

FIRST LINE TREATMENT IN PATIENTS RET+ MTC

Perioperative strategies

15Dec2023
MTC
CEA 829; CTN 31021





OXFORD

BJS, 2024, znae199
https://doi.org/10.1093/bjs/znae199
Guideline

European Society of Endocrine Surgeons (ESES) consensus statement on advanced thyroid cancer: definitions and management

The potential of novel therapies to reduce tumour volume is also paving the way for the use of these drugs in a neoadjuvant setting.

⇩

With the aim of improving oncological outcomes (complete resection; reducing comorbidity)

⇩

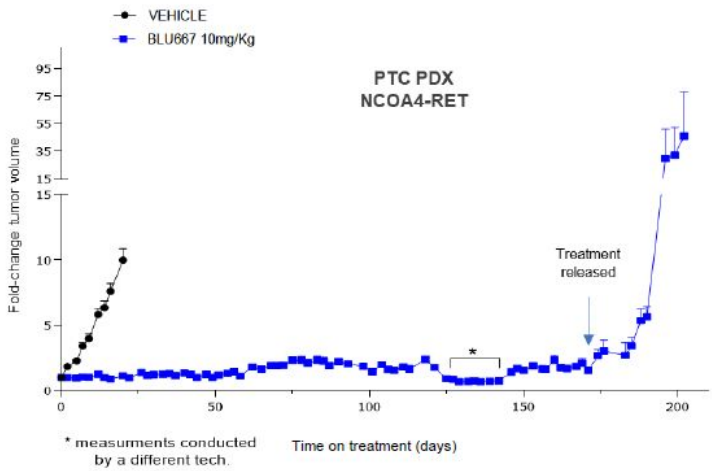
The need for evidence-based and competence-based decisions requires the assembly of a MDT to offer an individualized approach for each patient.

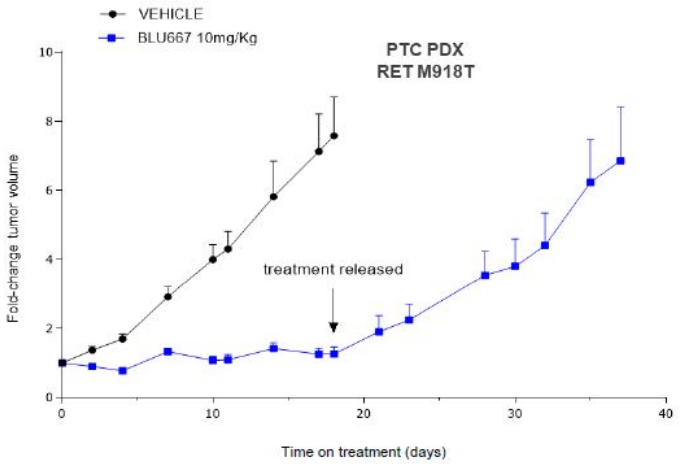
Jozhagi Y, et al. Head Neck. 2021 Jan;43(1):E7-E12.

FIRST LINE TREATMENT IN PATIENTS RET+ MTC

Treatment duration

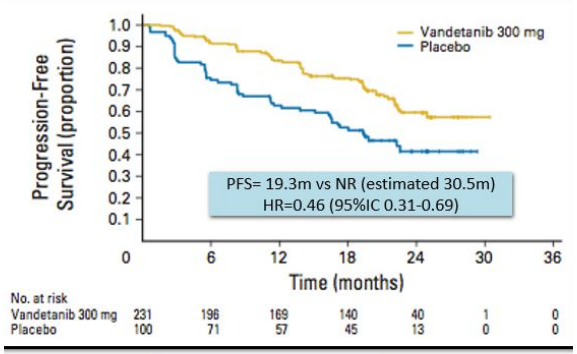
Both PDX models showed prolonged responses to BLU667 and experienced regrowth when the treatment was released



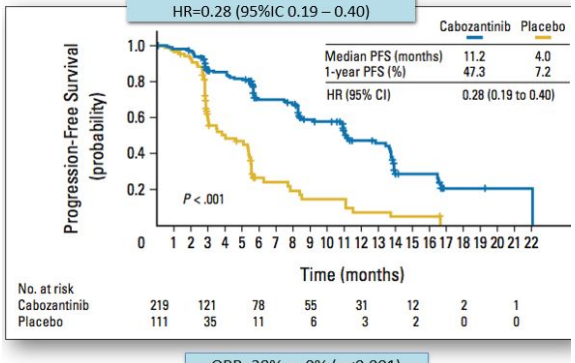


Álvarez García A, et al. Presented at ESMO 2023

FIRST LINE TREATMENT IN PATIENTS RET- MTC



ORR= 45% vs 13%, p<0.001



ORR=28% vs 0% (p<0.001)

- **Vandetanib should not be administered to patients in whom rearranged during transfection (RET) mutation status is not known or is negative.**
- **Restriction of the indication is based on data from the randomized study D4500C00058, and the observational study OBS14778, showing insufficient activity of vandetanib in patients with no identified RET mutations.**
- **Prior to initiation of treatment with vandetanib, the presence of a RET mutation should be determined by a validated test.**
- **For patients currently under treatment and for which the RET status remains unknown or is negative, healthcare professionals are recommended to discontinue treatment taking into account their judgement of the patients' clinical response and the best treatment available.**

N=79 patients (efficacy)

RET+ (N=58) vs RET- (N=21) with an ORR 42% vs 5%.

Wells S, *et al.* J Clin Oncol 2012;30:134–41
Elisei R, *et al.* J Clin Oncol 2014;32(17):1864
Schlumberger M, *et al.* Ann Oncol 2017;28:2813–9

THE PARTICULAR CHALLENGE OF SPAIN

Efficacy and safety of vandetanib for patients with advanced and progressive MTC as systemic treatment beyond first-line therapy

		Vandetanib 1st line (n=36)	Vandetanib 2nd line (n=13)	Vandetanib 3rd line (n=10)	All (n=59)
Sex (Male)		23 (63.9)	7 (53.8)	6 (60)	36 (61)
Age		54	40	59	48
ECOG	0 1 2	15 (41.7) 20 (55.6) 1 (2.7)	4 (30.8) 6 (46.2) 3 (23.1)	0 9 (90) 1 (10)	19 (32,2) 35 (59,3) 6 (10,2)
Origin	Hereditary Sporadic	2 (5.6) 34 (94.4)	1 (7.7) 12 (92.3)	1 (10) 9 (90)	4 (6,8) 55 (93,2)
RET status	Positive Negative Unknow	6 (16.7) 25 (69.4) 5 (13.9)	1 (7.7) 9 (69.2) 3 (23.1)	1 (10) 7 (70) 2 (20)	8 (13,6) 41 (69,5) 10 (16,9)
1st line	Vandetanib Sorafenib Sunitinib Cabozantinib Other TKI	36 (100) 0 0 0 0	0 8 (61.5) 3 (23.1) 0 2 (15.4)	0 5 (50) 2 (20) 1 (10) 2 (20)	36 (61) 13 (22) 5 (8.5) 1 (1.7) 4 (6.8)
2nd line	Vandetanib Sorafenib Sunitinib Cabozantinib Other TKI None	0 0 2 (5.5) 3 (8.4) 2 (5.5) 29 (80,6)	13 (100) 0 0 0 0 0	0 3 (30) 2 (20) 0 3 (30) 2 (2)	15 (25.4) 3 (5) 4 (6.7) 3 (5) 5 (8.4) 31 (52.5)
3rd line	Vandetanib Cabozantinib Other TKI None	0 0 0 36 (100)	0 4 (30.8) 2 (15.4) 7 (53.8)	10 (100) 0 0 0	10 (16.9) 4 (6.7) 2 (3.4) 43 (72.9)

All pts	Response by RECIST v1.1	ORR	DCR
1st line (n = 36)	2 CR, 15 PR, 18 SD, 1 PD	47.2%	97.2%
2nd line (n = 13)	1 CR, 6 PR, 4 SD, 2 PD	53.8%	84.6%
3rd line (n = 10)	4 PR, 4 SD, 2 PD	40%	80%

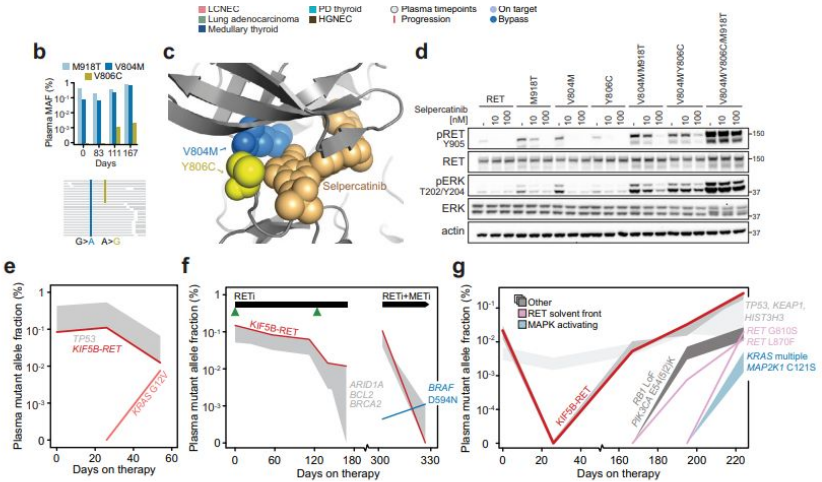
RET-	Response by RECIST v1.1	ORR	DCR
1st line (n = 23)	1 CR, 9 PR, 12 SD, 1 PD	43.4%	95.6%
2nd line (n = 11)	1 CR, 4 PR, 4 SD, 2 PD	45.4%	81.8%
3rd line (n = 7)	4 PR, 2 SD, 1 PD	57.1%	85.7%

Hernando Cubero J, et al. ESMO 2018: #43278

WHAT TO DO AT DISEASE PROGRESSION?

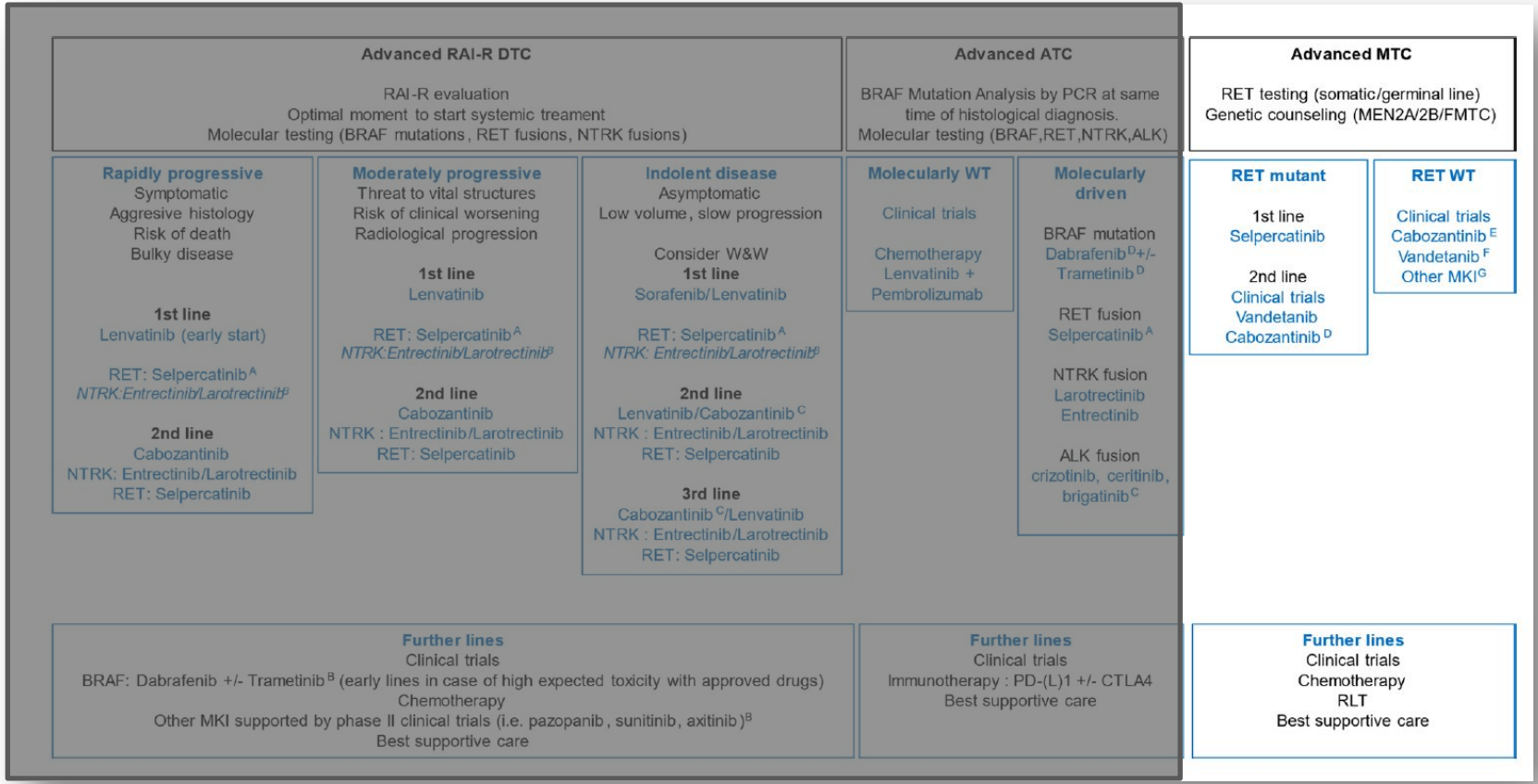
RET+

Drug		Mechanism of action / Data and recruitment	NCT identifier
TPX-0046	RET/SRC inhibitor		NCT04161391
Vepafesitinib (TAS0953/HM06)	Next gen. RET inhibitor	Preclinical [on-target resistance mutations (variants in RETL730, RETV804 and RETG810), and properties in the brain]	NCT04683250
LOXO-260	Next gen. RET inhibitor	Phase I (RETV804M/L, RETG810C/R/S)	NCT05241834
TY-1091	Next gen. RET inhibitor	Preclinical	



Niu Ch, et al. Cancer Res (2023) 83 (7_Supplement): 3419; Rosen EY, et al. Nat Commun. 2022; Miyazaki I, et al. Nature Cancer 2023; 4: 1345–1361

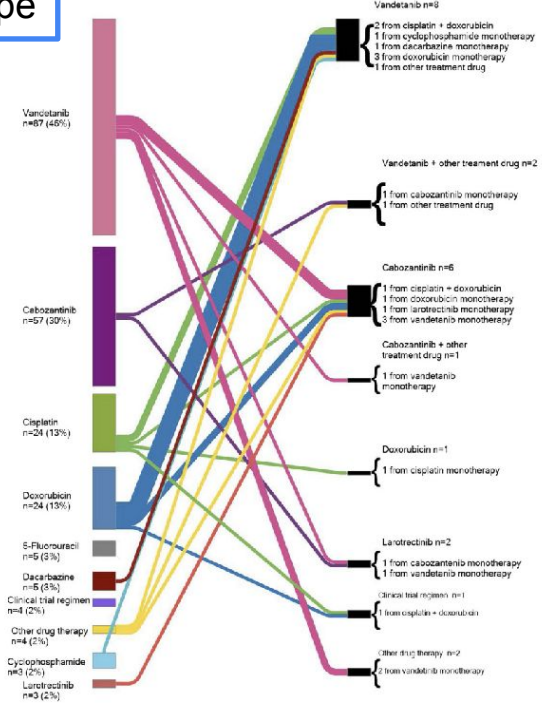
WHAT TO DO AT DISEASE PROGRESSION?



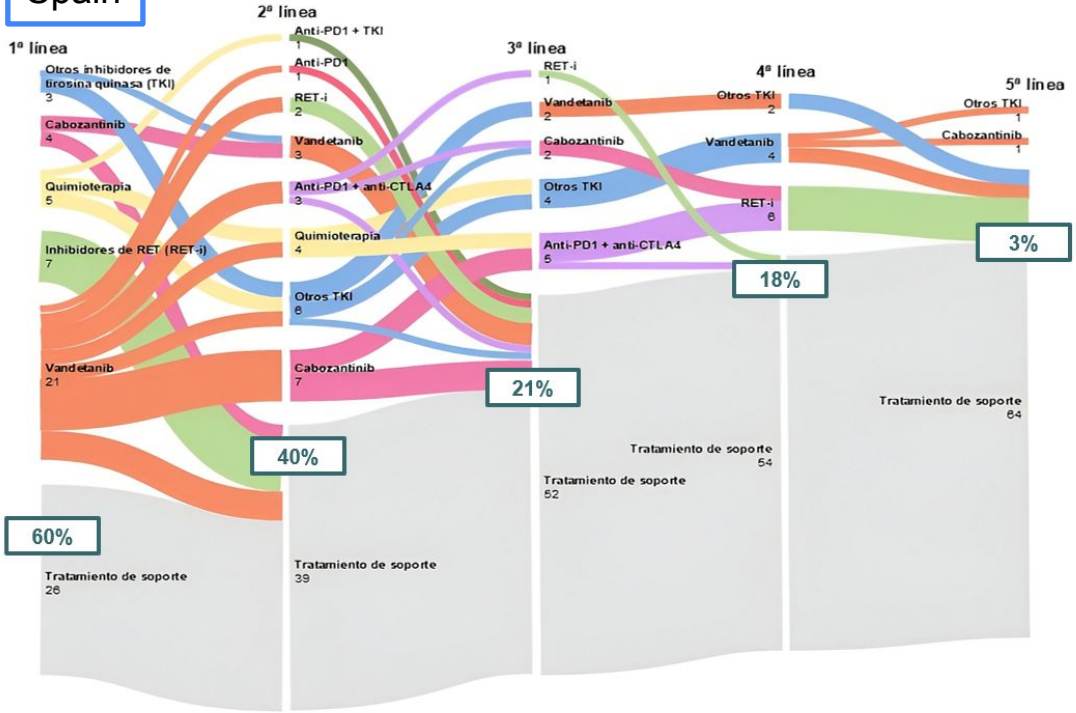
Alonso-Gordoa T. SEOM-GETNE-TTCC Clinical guideline thyroid cancer (2023). Clin Transl Oncol. 2024 Nov;26(11):2902-2916.

TREATMENT SEQUENCING:
Lack of scientific data and Real Clinical Practice

Europe



Spain



González Merino C, et al. Presented at SEOM 2025

TREATMENT SEQUENCING:
Lack of scientific data and Real Clinical Practice

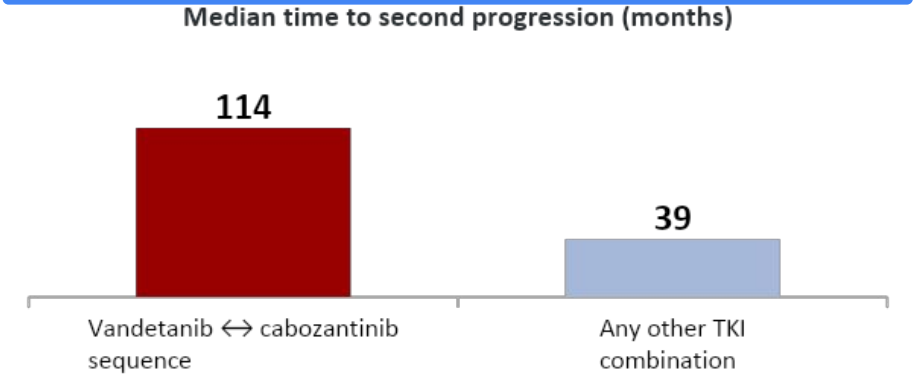
Germany · retrospective · n=48

26% vs 22%
ORR: vandetanib (n=47) vs cabozantinib (n=23)

17 vs 4 months
Median PFS (vandetanib vs cabozantinib; mostly 1L vandetanib, 85%)

33% vs 31%
ORR in second line: vandetanib vs cabozantinib

Turkish Oncology Group 2026 · retrospective · n=115



Median PFS by line
1L: vandetanib 40.8 mo · cabozantinib not reached · chemotherapy 4.9 mo
2L: cabozantinib not reached · vandetanib 32.5 mo

No prospective sequencing data: second-line activity in both directions, but evidence is retrospective.

Koehler VF, et al. Thyroid 2021 (real-world efficacy and safety of cabozantinib and vandetanib in advanced MTC); Turkish Oncology Group. J Clin Med 2026;15(6):2353. Cross-study comparisons are not valid.

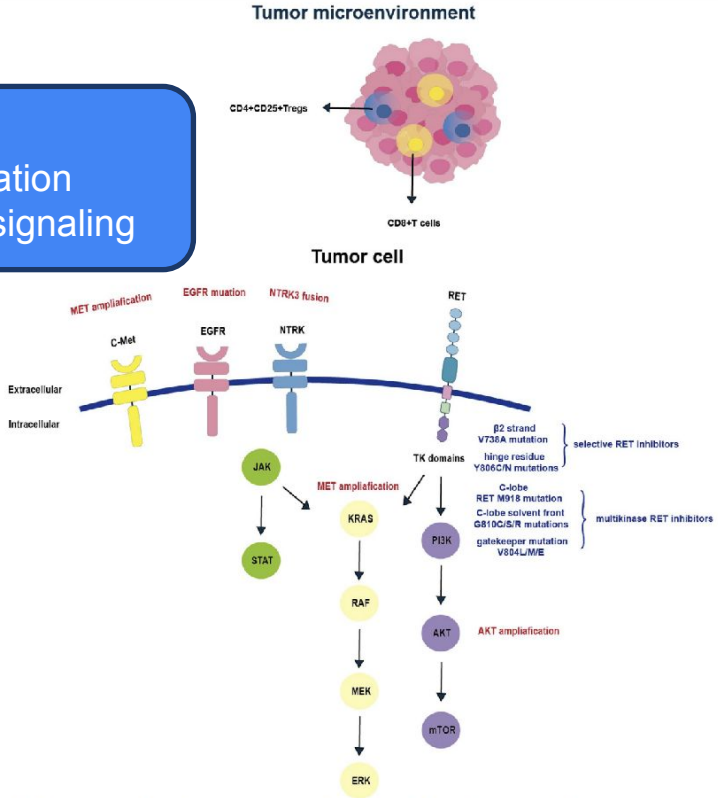
TREATMENT SEQUENCING:
Lack of scientific data and Real Clinical Practice

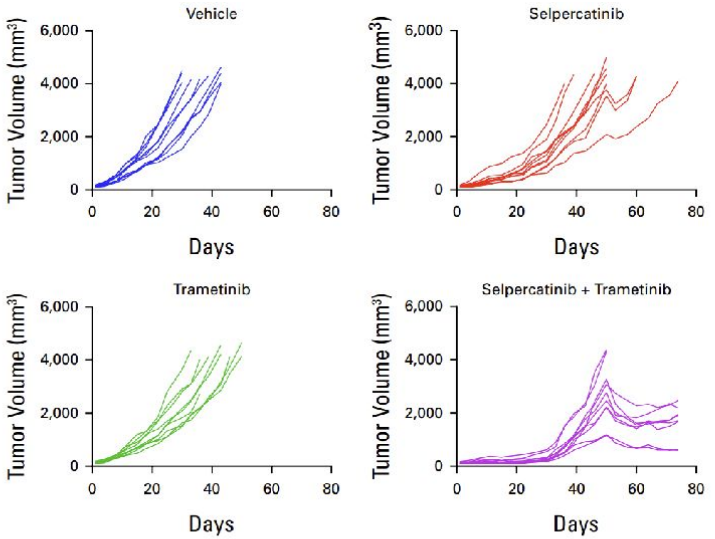
Therapy	Study (design)	Population	N (MTC)	ORR
Lenvatinib	Phase II	Unresectable, progressive MTC (RECIST 1.0, ≤12 mo); 44% prior anti-VEGFR	59	**36% (95% CI 24–49); mPFS 9.0 mo**
Sunitinib	THYSU, Phase II	Advanced DTC/ATC/MTC, no prior anti-angiogenic therapy; MTC subgroup	26 (of 71)	**38.5% (95% CI 22.6–56.4)**
Radioligand therapy	Retrospective	^{177}Lu-octreotate; progressive MTC (80% RECIST PD), high SSTR uptake in 70%	10	**0% (SD 40%); mPFS 0.7 y**
	Case series	SSTR-PET+ metastatic MTC	6 treated	**33% (2 PR); 2 SD; 2 PD**
Local therapies	Case series	Liver metastases (retrospective series)	12; 11; 7	**PR 5/12 (42%); 5/11 (45%); 7/7**
	Case series	Liver metastases, multiple	8	**63% (1 CR + 4 PR)**
	Case series	Liver metastases	9; 11; 6	**Not reported (local ablation)**
Chemotherapy	DTIC + 5-FU	Locally advanced / metastatic MTC	5	**60% (3 PR)**
	Doxorubicin-STZ / 5-FU-DTIC alternating	Metastatic MTC	20	**15% (3 PR); SD 50%**

Schlumberger M, et al. Clin Cancer Res 2016; Ravaud A, et al. Eur J Cancer 2017; Beukhof CM, et al. BMC Cancer 2019; Fromigué J, et al. 2006; Lorenz K, et al. 2005; Grozinsky-Glasberg S, et al. 2017; Puleo 2022; Schlumberger M, et al. Ann Oncol 1995; Nocera M, et al. Br J Cancer 2000. Cross-trial comparisons; small, mostly retrospective series.

TREATMENT SEQUENCING:
Underlying biology in treatment resistances

TME
RET alteration
Bypass RET signaling





Milewski D, et al. JCO Precis Oncol. 2026 Jun;10(6):e2600091.

TREATMENT SEQUENCING:
Underlying biology in treatment resistances

HIGH GRADE

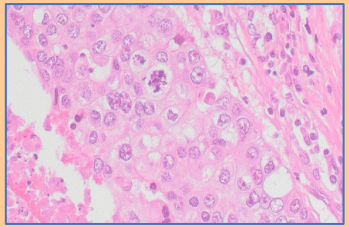
Mitotic count
≥5 mitosis/2mm²

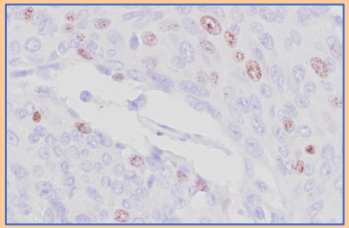
and/or

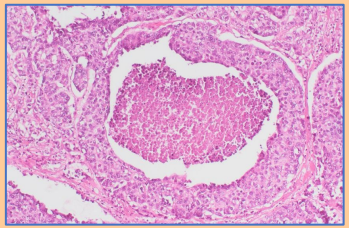
Proliferation index
Ki-67 ≥5%

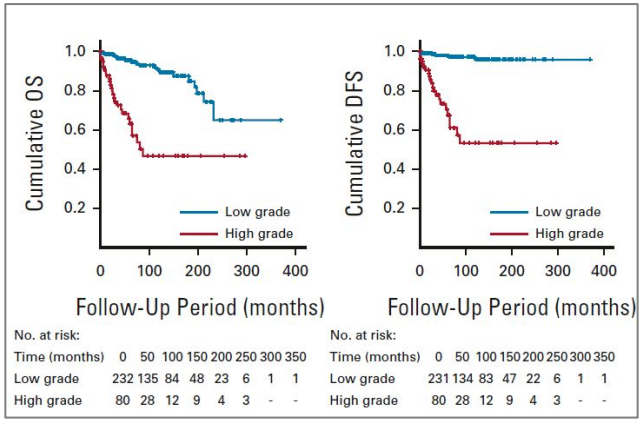
and/or

Necrosis







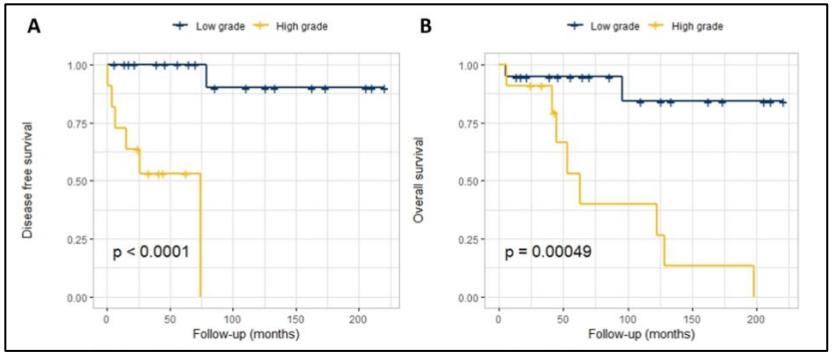


No. at risk:

Time (months)	0	50	100	150	200	250	300	350
Low grade	232	135	84	48	23	6	1	1
High grade	80	28	12	9	4	3	-	-

No. at risk:

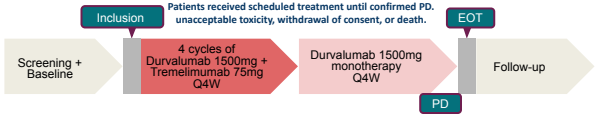
Time (months)	0	50	100	150	200	250	300	350
Low grade	231	134	83	47	22	6	1	1
High grade	80	28	12	9	4	3	-	-

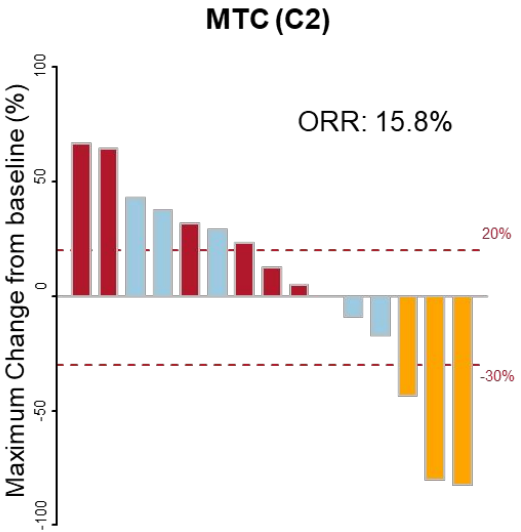


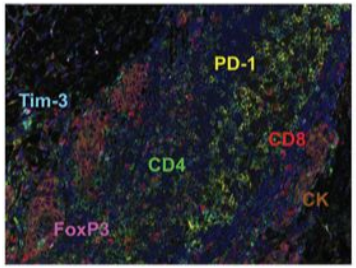
Ruz Caracuel I, et al. Endocr Pathol. 2024 Sep;35(3):207-218; Xu B, et al. J Clin Oncol. 2022;40(1):96-104

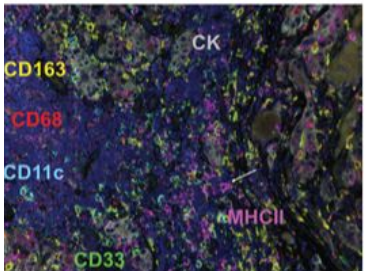
NOVEL DRUGS

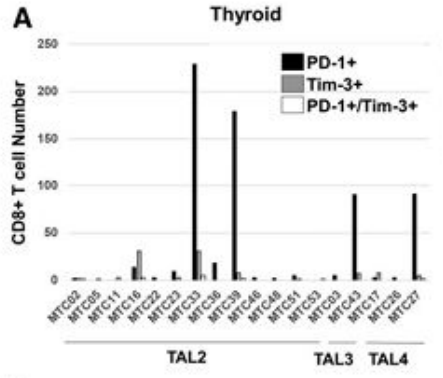
IMMUNOTHERAPY











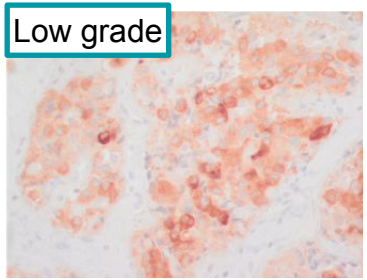
García Álvarez A, et al. Front Endocrinol (Lausanne). 2022 Aug 5:13:929091; Capdevila J, et al. Presented at ESMO Congress 2023; Pozeyev N, et al. Thyroid. 2020 Sep;30(9):1263-1279.

NOVEL DRUGS

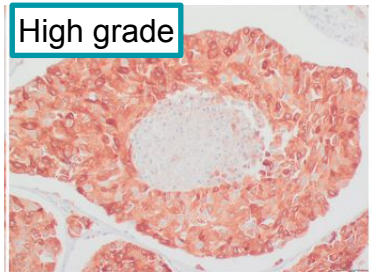
DLL3 TARGETED DRUGS

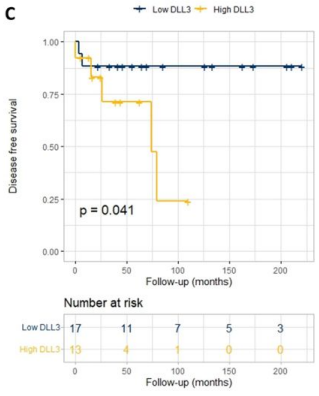
DLL3

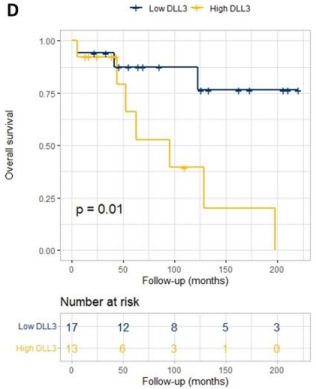
Low grade



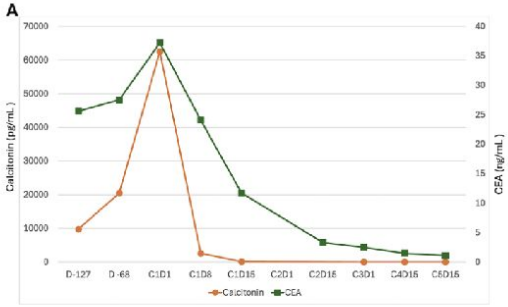
High grade

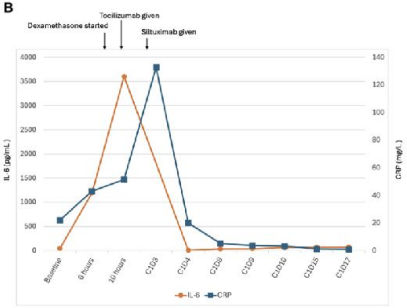






Case series in refractory patients





Ongoing trials

Phase II basket trial · NCT06788938 ·

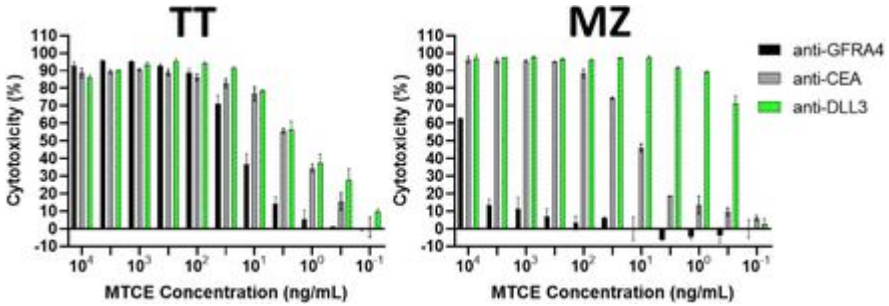
ELIGIBILITY

Advanced DLL3+ tumors incl. NENs (other than SCLC or NEPC)
≥1 prior line if standard of care exists

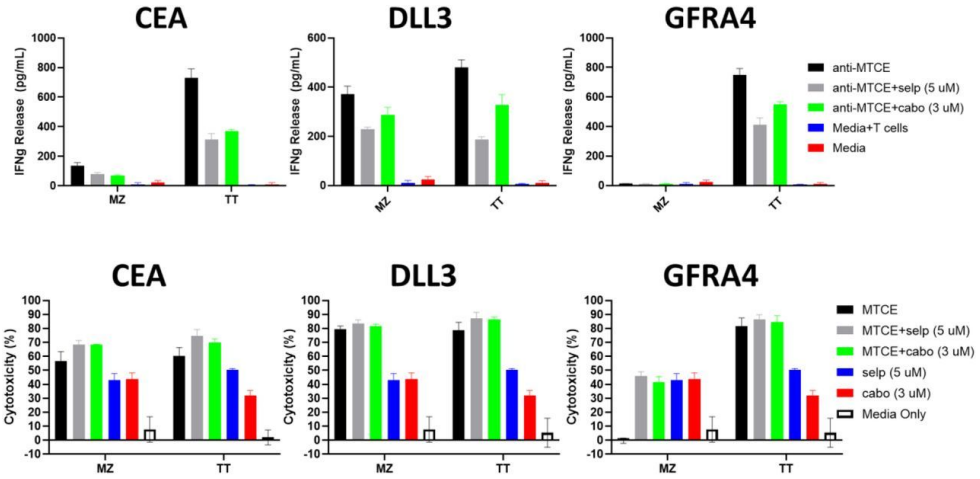
Ruz Caracuel I, et al. Endocrine Pathology (2024) 35:207–218
www.clinicaltrials.gov
Roberts TJ, et al. Thyroid. 2026 Jun;36(6):682-687.

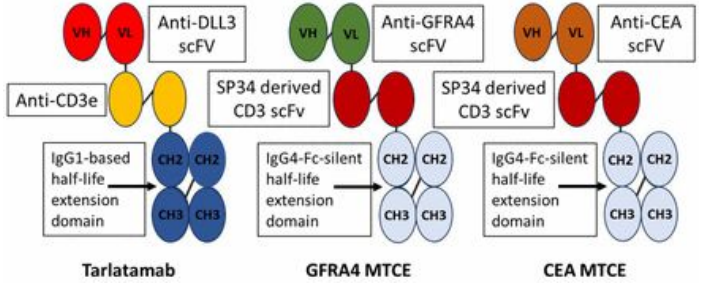
NOVEL DRUGS: Against CEA, GFRA4, DLL3

Concentration-dependent cytotoxicity of MTCEs against the MZ and TT MTC cell lines at a 1:1 E:T ratio.



Effect of Combining TKIs with MTCEs. TKIs moderate IFNγ secretion, while numerically increasing cytotoxicity.





NOVEL DRUGS

GFRα4 CAR-T CELLS IN MTC

T-cell collection
autologous T cells

→

CAR-T manufacture
lentiviral anti-GFRα4 scFv

→

Lymphodepletion
fludarabine + cyclophosphamide

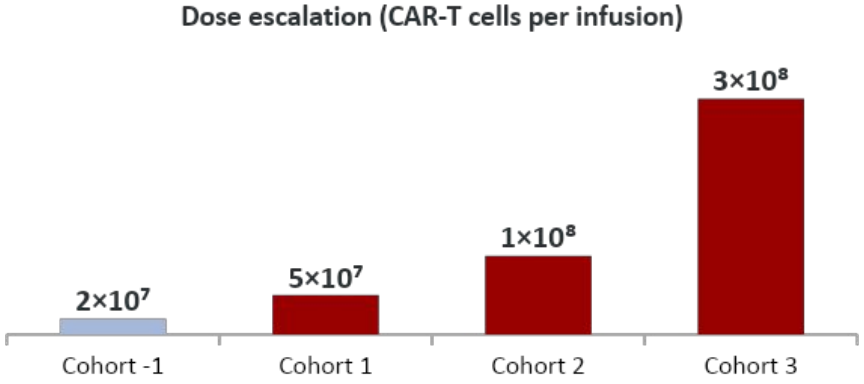
→

CAR-T infusion
IV, 4 dose levels

→

Follow-up
safety up to 15 years

NCT04877613



TARGET
GFRα4: expressed in MTC, independent of RET status

POPULATION
Progressive MTC after ≥1 prior TKI · ECOG 0–1 · RECIST-evaluable disease

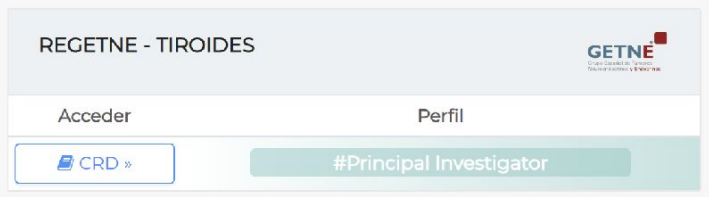
ENDPOINTS
Primary: TEAEs (CTCAE v5.0). Secondary: manufacturing success, ORR, DoR, PFS, OS

ClinicalTrials.gov NCT04877613: Phase I trial of GFRα4 CAR T cells in adult patients with recurrent or metastatic medullary thyroid cancer. Cohen RB, University of Pennsylvania.

CONCLUSIONS

- ✔ Over the past few years, substantial advances have been achieved in the molecular characterization of MTC.
- ✔ Nevertheless, access to targeted therapeutic options remains limited, particularly in Spain.
- ✔ The RET oncogene plays a pivotal role in the pathogenesis of MTC, and its inhibition has enabled the development of highly selective inhibitors, such as selpercatinib, which have significantly altered the natural history of this malignancy and led precision oncology into the management of MTC.
- ✔ Defining the optimal strategies at disease progression and identifying additional actionable targets remain key unmet needs that require evidence-based answers in the very near future.





September, Thyroid Cancer Awareness Month