PERFILES MOLECULARES: NUEVAS DIANAS Y OPORTUNIDADES TERAPÉUTICAS

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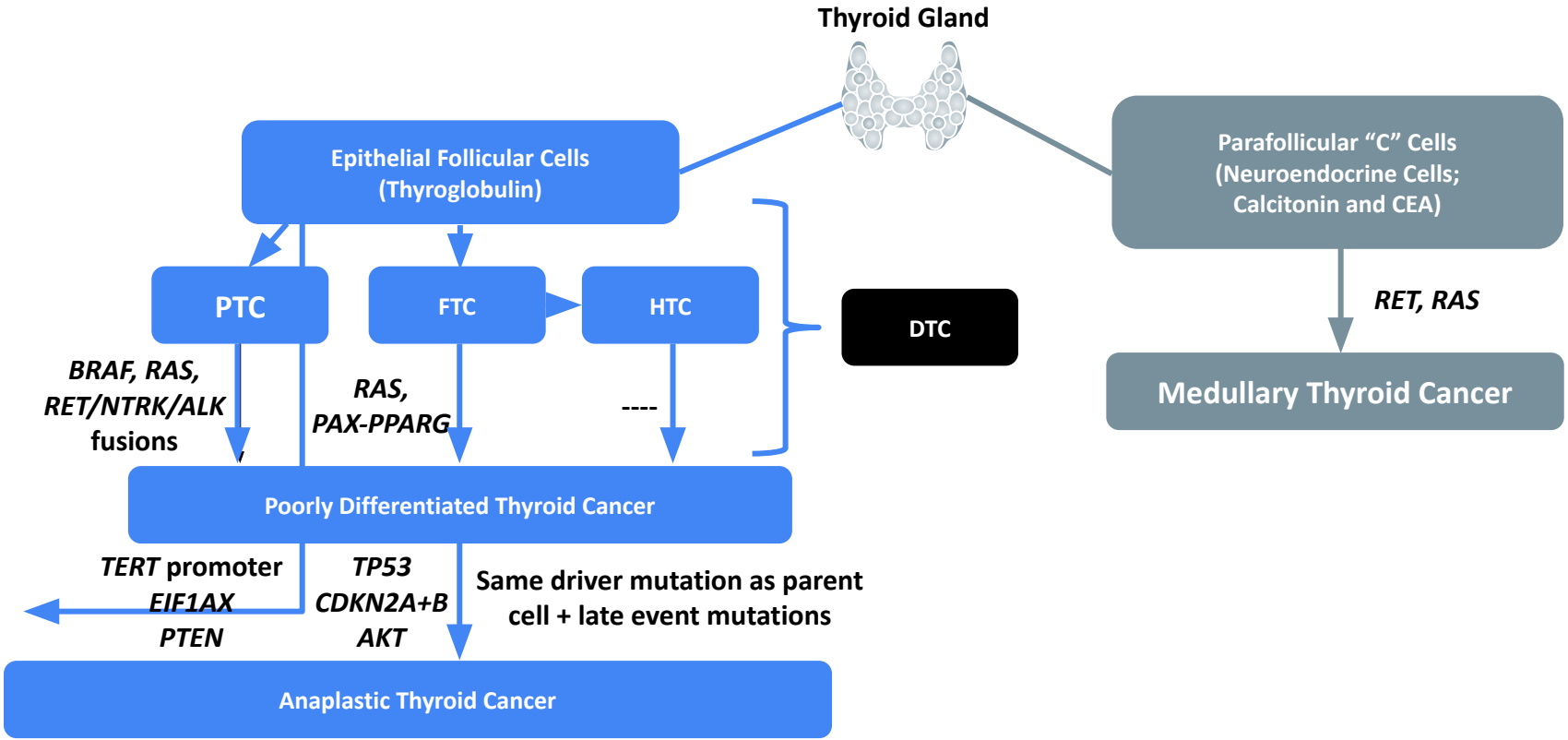
Declaración de conflicto de intereses

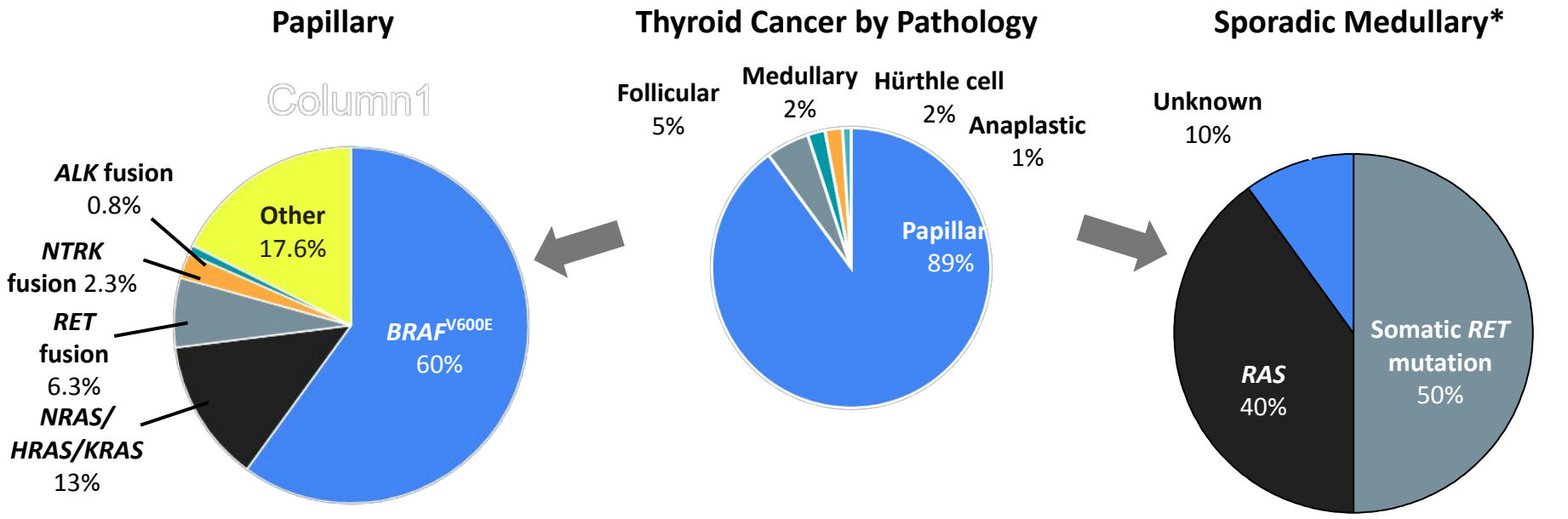
- *Employment:* Consorci Corporació Sanitària Parc Taulí / AIALE, S.A. – Hospital de Barcelona.
- *Consultant or Advisory Role:* Sanofi, Janssen, Astellas, Bayer, Ipsen, Pfizer, Roche, Novartis, Eisai, EUSA Pharma, BMS, MSD, AstraZeneca, Merck, Rovi, Daiichi Sankyo, Techdow, Lilly, Advanced Accelerator Applications.
- *Speaking:* Astellas, Janssen, Sanofi, Bayer, Ipsen, Pfizer, Roche, BMS, Rovi, Daiichi Sankyo, Leo Pharma, Eisai, Boehringer Ingelheim, Merck, EUSA Pharma, Lilly, Advanced Accelerator Applications.
- *Grant support:* Astellas, Janssen, Sanofi, Bayer, Ipsen, Ferrer, Pfizer, Roche, GSK, BMS.
- *Travel/acommodation expenses:* Astellas, Janssen, Sanofi, BMS, Bayer, Ipsen, Roche, Novartis, Pierre Fabre, Pfizer, Eisai.

INTRODUCTION

ORIGIN OF THYROID CANCERS



Mutation Spectrum in Thyroid Cancer



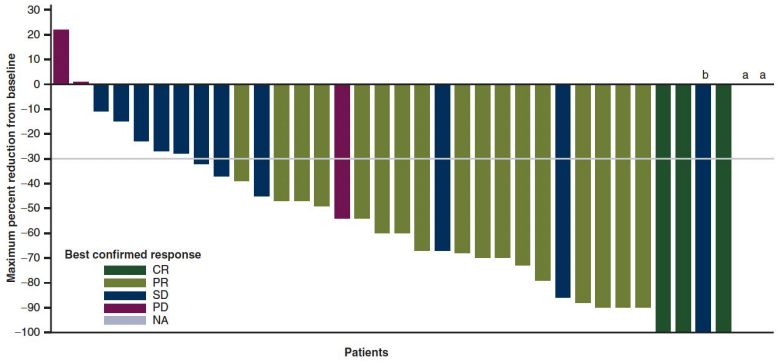
*Familial MTC: 100% germline *RET* mutation.

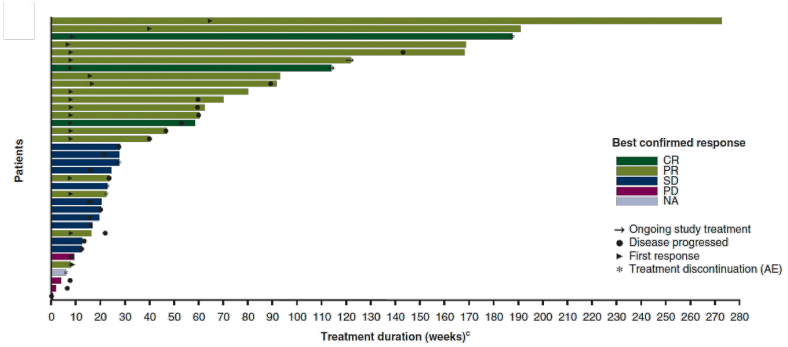
Thyroid cancers are rich in druggable targets

TCGA. Cell 2014;159:676-690. SEER, SEER cancer statistics review (CSR) 1975-2014. Raue F, et al. Clin Cancer Res. 2016;22(20):5012-5021.

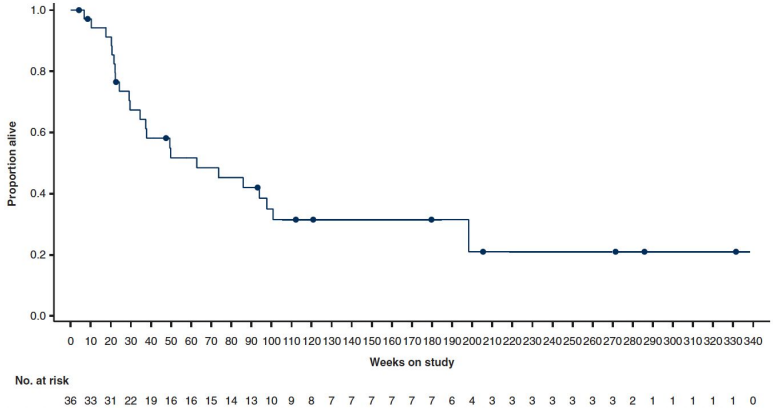
BRAF

Dabrafenib plus trametinib in patients with *BRAF* V600E-mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study





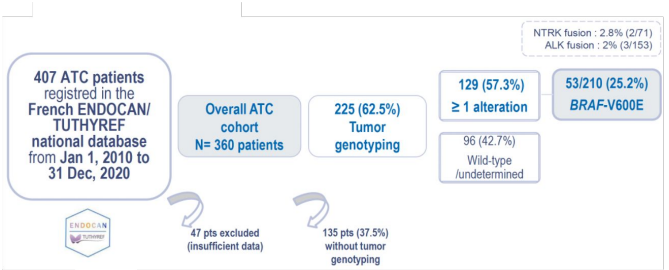
- N=36
- **ORR (investigator): 56% (95% CI, 38.1-72.1)**
- 12-mo DoR: 50%
- Median OS: 14.5 mo
- 12-mo PFS: 43.2%
- 12-mo OS: 51.7%
- 24-mo OS: 31.5%
- FDA-approval: May 2018

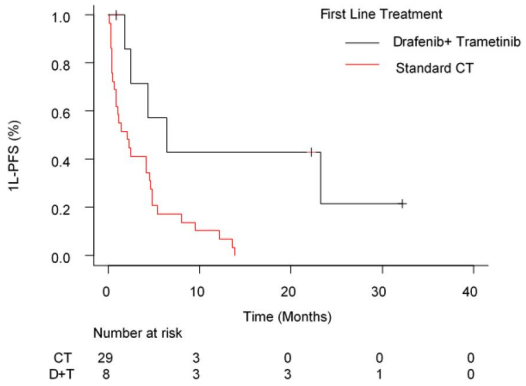


Subbiah V, et al. Ann Oncol 2022 Apr;33(4):406-415

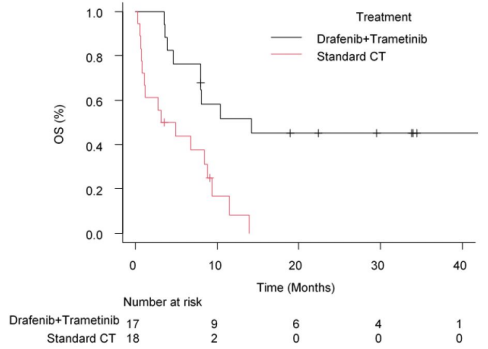
BRAF-V600E anaplastic thyroid carcinoma: clinical characteristics and outcome with *BRAF* inhibitors and chemotherapy in real-life practice: a multicentric retrospective study of the French ENDOCAN TUTHYREF network (Abstract #5197)

PARIS 2022 ESMO congress





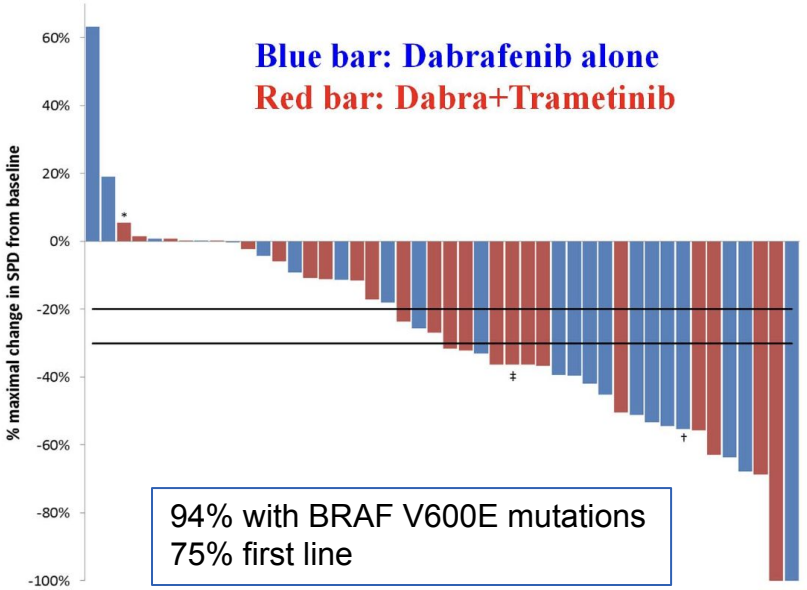
Median L1-PFS (months)
Dabrafenib +Trametinib (n=8) : 6.38 (1.79-NA)
Standard CT (n=29): 2.15 (0.66 -4.56)

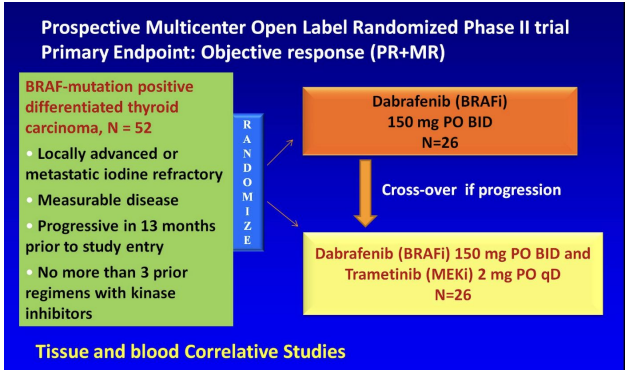


Median OS (months)
Dabrafenib +Trametinib (n=17) : 14.21 (4.66-NA)
Vemurafenib (n=4) : 14.91 (6.88-NA)
Standard CT (n=18) : 4.05 (0.83-8.83)
No CT : 1.31 (0.56-NA)

de la Fouchardière C, et al. Ann Oncol 2022;33 (suppl_7): S750-S757. 10.1016/annonc/annonc1077

OSU 12064: A Randomized Phase 2 Study of single agent Dabrafenib (BRAFi) vs. combination regimen Dabrafenib (BRAFi) and Trametinib (MEKi) in patients with BRAF mutation or BRAF gene fusion defect in thyroid carcinoma





	Arm A (n = 26) Dabrafenib	Arm B (n = 27) Dabrafenib + Trametinib	p-value
Assessable pts (n)	22	24	
Partial response	10	9	
Minor response (MR)*	1	4	
Objective Response	11/22 (50%)	13/24 (54%)	0.78
Stable disease	9	10	
Progressive disease	2	1	
Median Progression Free Survival (months) (95% CI)	11.4 (3.8 – NR)	15.1 (11.7 –NR)	0.27
Median Duration of response (months) (95% CI)	15.6 (4.2 – NR)	13.3 (9.7 – NR)	0.87

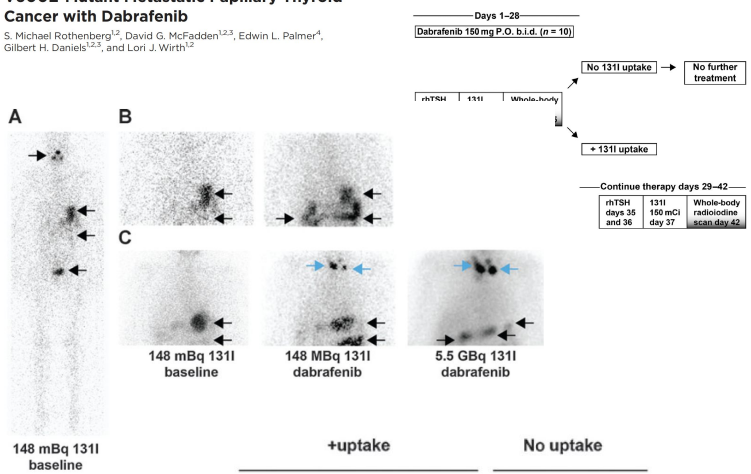
Shah MH, et al. J Clin Oncol 2017;35(suppl; abstr 6022). DOI: 10.1200/JCO.2017.35.15_suppl.6022

Cancer Therapy: Clinical

Clinical Cancer Research

Redifferentiation of Iodine-Refractory *BRAF* V600E-Mutant Metastatic Papillary Thyroid Cancer with Dabrafenib

S. Michael Rothenberg[1,2], David G. McFadden[1,2,3], Edwin L. Palmer[4], Gilbert H. Daniels[1,2,3], and Lori J. Wirth[1,2]

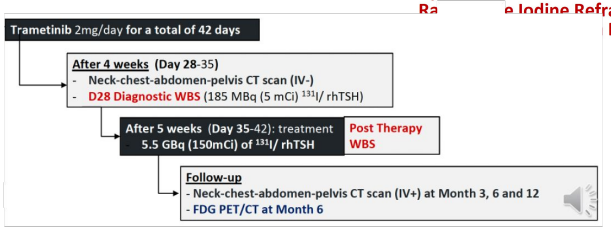


Rothenberg SM, et al. Clin Cancer Res 2015 Mar 1;21(5):1028-35

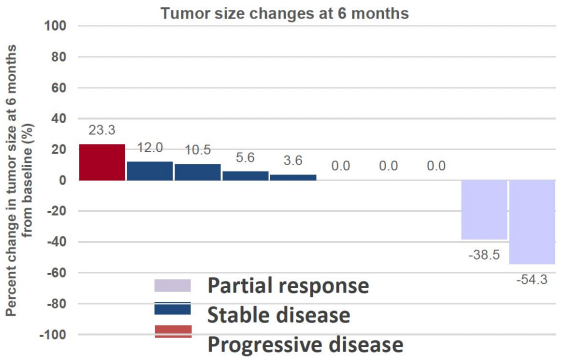
2021 ESMO congress

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

MERAIODE:
A Redifferentiation Phase II Trial With Trametinib Followed by Radioactive Iodine Administration for Metastatic Ra… e Iodine Refractory Differentiated Thyroid … RAS Mutation



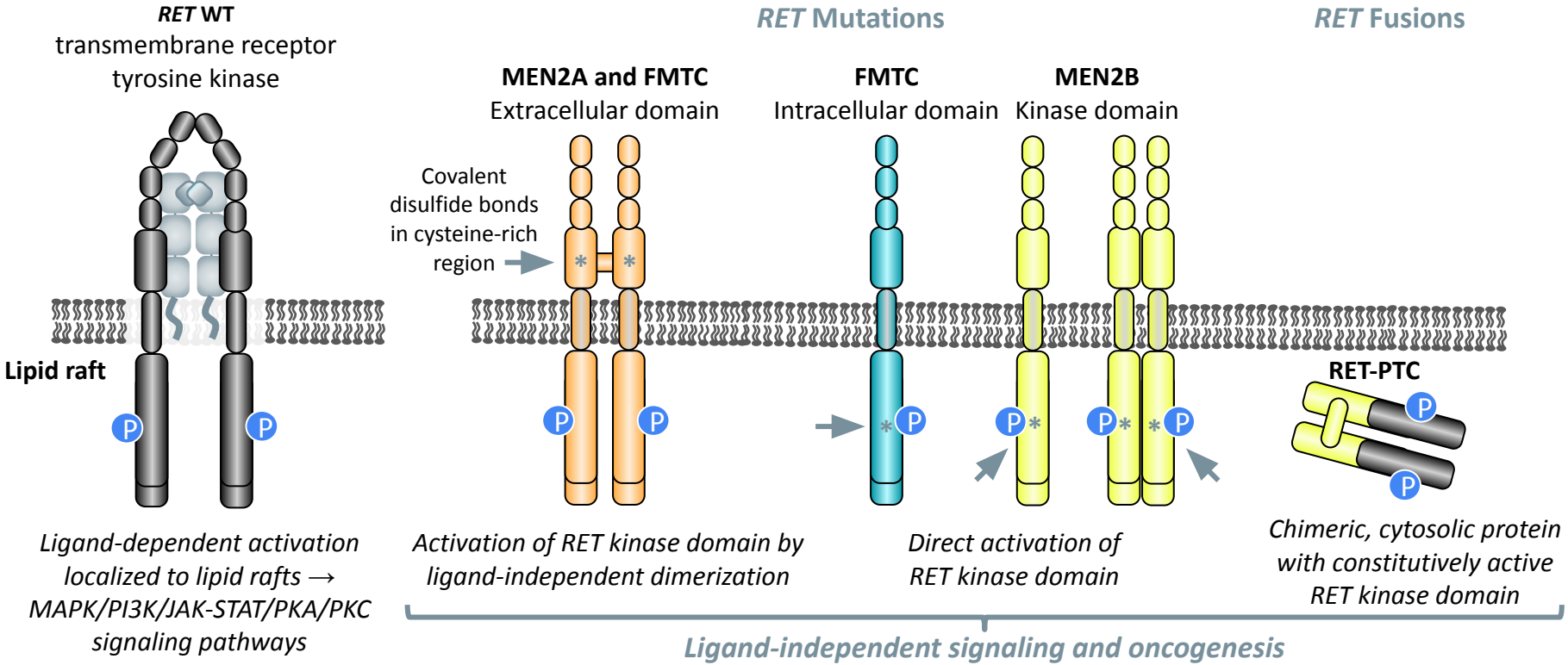
N/Total % (95% CI)		
Baseline- Diagnostic1 WBS	Day 28- Diagnostic2 WBS	Day 35- Post-therapy WBS
3/10 **30%** [$CI_{95\%}$: 7-65]	**4/9** **44 %** [$CI_{95\%}$: 14-79]	**6 /10** **60%** [$CI_{95\%}$: 26-88]



Leboulleux S, et al. Ann Oncol 2021;32(suppl_5): S1205-S1210. 10.1016/annonc/annonc715

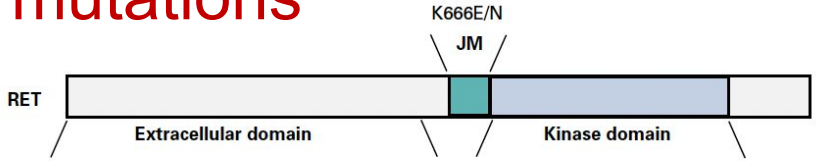
RET

Two Major Mechanisms of *RET* Proto-Oncogene Activation in Thyroid Cancer: *RET* Mutations and *RET* Fusions



Subbiah V, et al. Cancer Discov 2020;10:498. Wells SA, et al. Thyroid 2015;25:567-610.

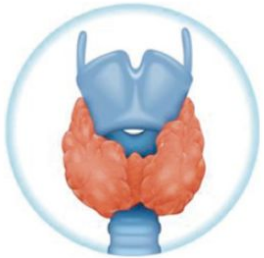
RET mutations



V292M	C618G/R/S/Y	E734A	A883F/T
E505_G506del	C620R/S/Y	E768D	R886W
A510V	L629_D631delinsH	V804L/M	S891A
E511K	C630F/R/Y	E805K	S904F
C515S/W	D631_R635delinsG	Y806C	R912A/P
C531R	D631Y	R833C	M918T
G533C	E632_L633del	M848T	A919P
K603Q	L633_C634dup	I852M	
Y606C	C634_R635insHELC		
C609R/S/W/Y	C634F/G/L/R/S/W/Y		
C611W/Y	T636M		
E616Q			

Somatic RET mutations in sporadic MTC

RET mutation	Frequency among somatic RET mutations in MTC (%, n = 850)
M918T	70.5
C634R	4.8
A883F	2.2
C634Y	2.1
C634W	1.9
C630R	1.5
E632_L633del	1.4
D898_E901del	1.4
C620R	0.6
S891A	0.6



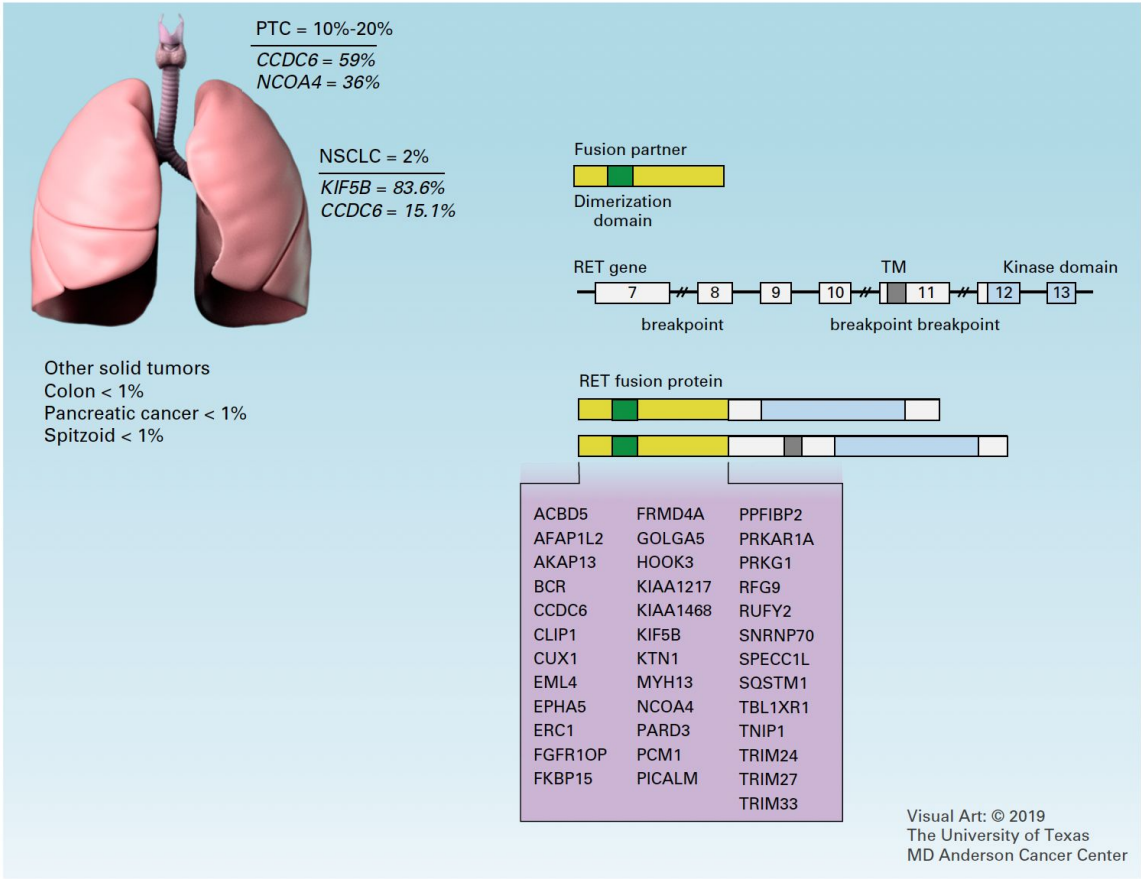
MTC

***RET* mutations among different MEN2 phenotypes**

Codon	Frequency of families with RET mutations (%)		
	MEN2A (n = 196)	MEN2B (n = 37)	FMTC (n = 265)
C515			0.4
C609	2.6		2.3
C611	0.5		1.1
C618	4.1		8.7
C620	5.6		7.2
C630			3.0
E632			0.4
C634	84.2		12.5
V648			0.8
K666			0.8
E768	0.5		4.9
L790			6.0
Y791			1.1
V804	1.5		30.6
R833			0.4
M848			0.8
A883			1.1
S891			12.5
S904			0.8
M918		97.3	1.1

Subbiah V, et al. J Clin Oncol 2020 Apr 10;38(11):1209-1221

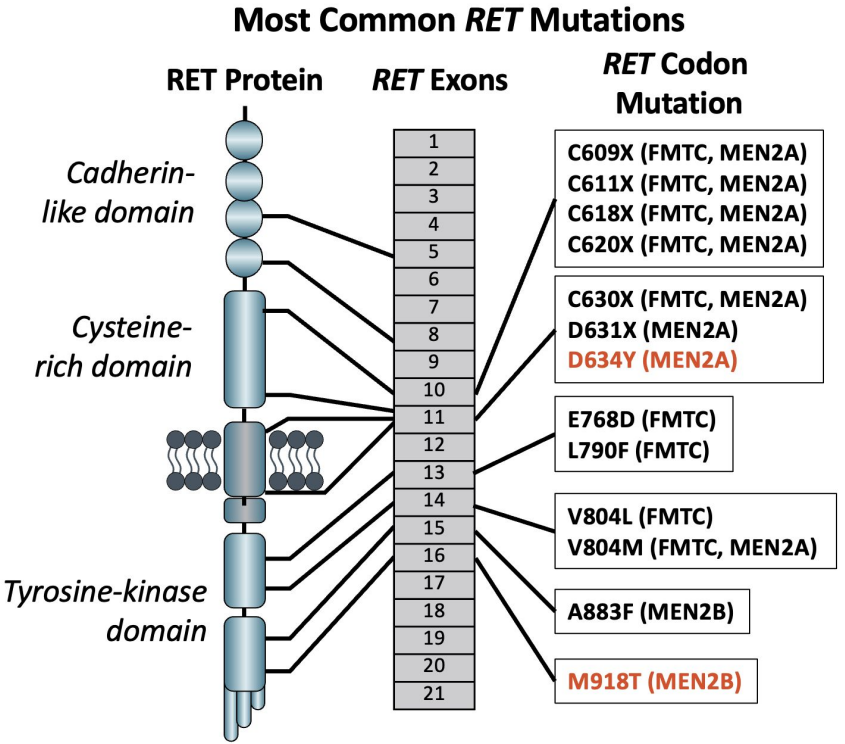
RET fusions



Subbiah V, et al. J Clin Oncol 2020 Apr 10;38(11):1209-1221

RET Mutations in Medullary Thyroid Carcinoma

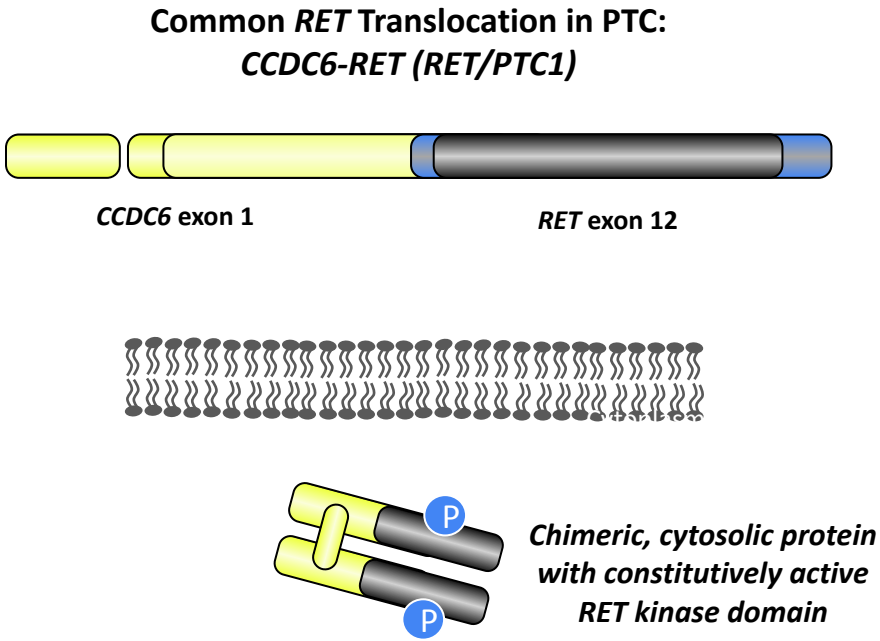
- *RET* gain-of-function mutation is main oncogenic driver in MTC
  - >100 reported
- Sporadic or nonfamilial MTC (70%-80%)
  - ~50% with somatic *RET* mutations
    - *RET* M918T most common
- Hereditary MTC (20%-30%)
  - >90% with germline *RET* mutation
    - MEN2B: *RET* M918T most common
    - MEN2A: *RET* C634X most common



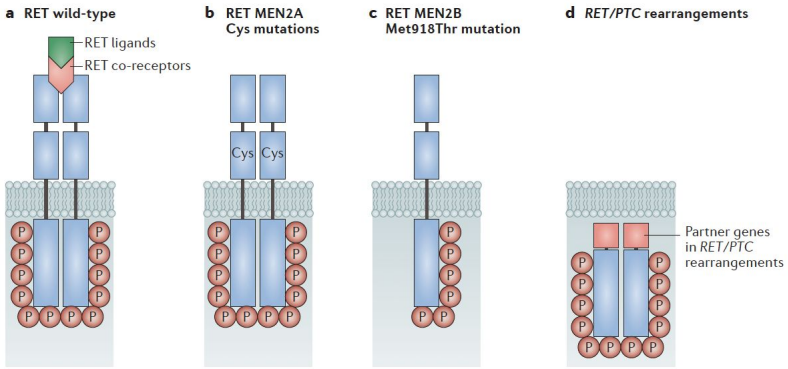
Santoro M, et al. Cold Spring Harb Perspect Biol 2013;5:a009233. Wells SA, et al. Thyroid 2015;25:567-610.

RET Fusions in Papillary Thyroid Carcinoma

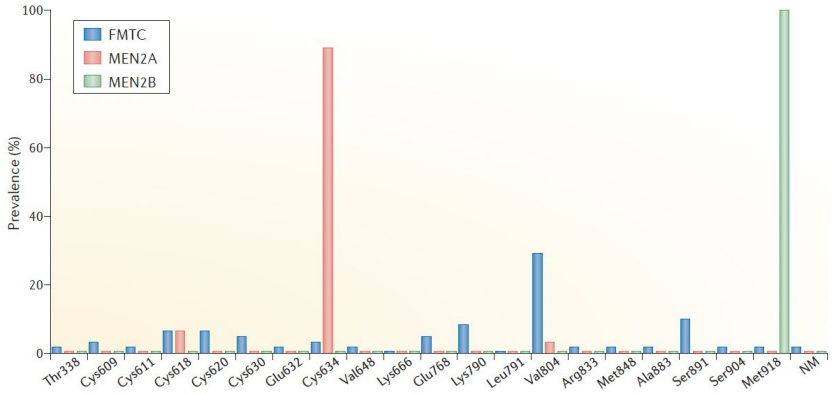
- *RET* fusions found in <10% of PTCs
  - More frequent in pediatric and AYA patients: ~30%
  - 58% in pediatric Chernobyl-induced cancers
- 90% accounted for by *CCDC6-RET (RET/PTC1), NCOA4-RET (RET/PTC3)*
  - >20 5' fusion partners described
- Also, can be present in PDTC, ATC



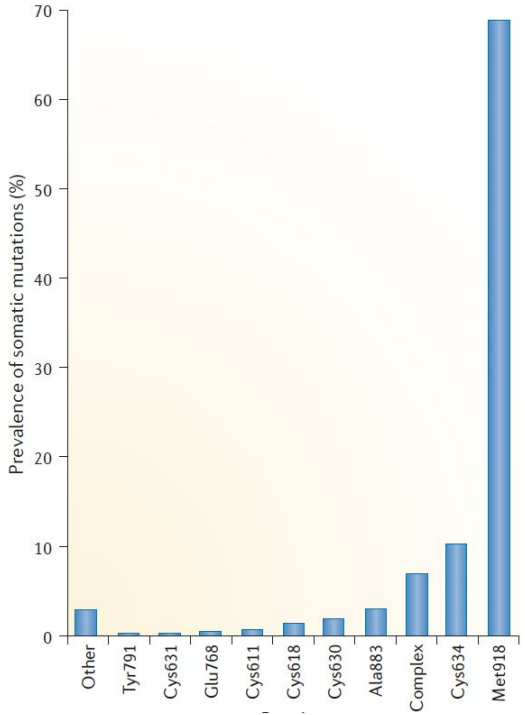
TCGA. Cell 2014;159:676-690. Thein KZ, et al. Trends Cancer 2021 Dec;7(12):1074-1088. Santoro M, et al. Genes (Basel) 2020;11:424. Mejia Saldarriaga M, et al. Front Oncol 2019;9:1303. Ricarte-Filho JC, et al. J Clin Invest 2013;123:4935.



RET mutations in hereditary MTC



RET mutations in sporadic MTC



Romei C, et al. Nat Rev Endocrinol 2016 Apr;12(4):192-202

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

L.J. Wirth, E. Sherman, B. Robinson, B. Solomon, H. Kang, J. Lorch, F. Worden, M. Brose, J. Patel, S. Leboulleux, Y. Godbert, F. Barlesi, J.C. Morris, T.K. Owonikoko, D.S.W. Tan, O. Gautschi, J. Weiss, C. de la Fouchardière, M.E. Burkard, J. Laskin, M.H. Taylor, M. Kroiss, J. Medioni, J.W. Goldman, T.M. Bauer, B. Levy, V.W. Zhu, N. Lakhani, V. Moreno, K. Ebata, M. Nguyen, D. Heirich, E.Y. Zhu, X. Huang, L. Yang, J. Kherani, S.M. Rothenberg, A. Drilon, V. Subbiah, M.H. Shah, and M.E. Cabanillas

Wirth LJ, et al. N Engl J Med 2020;383:825-835

Table 2. Efficacy.*

Response	*RET*-Mutant MTC Previously Treated		*RET*-Mutant MTC Not Previously Treated		Previously Treated *RET* Fusion–Positive Thyroid Cancer	
	Independent Review (N=55)	Investigator Assessment (N=55)	Independent Review (N=88)	Investigator Assessment (N=88)	Independent Review (N=19)	Investigator Assessment (N=19)
Objective response — % (95% CI)	69 (55–81)	62 (48–75)	73 (62–82)	71 (60–80)	79 (54–94)	58 (34–80)
Best response — no. (%)						
Complete response	5 (9)	3 (5)	10 (11)	3 (3)	1 (5)	0
Partial response	33 (60)	31 (56)	54 (61)	59 (67)†	14 (74)	11 (58)
Stable disease	14 (25)	16 (29)	20 (23)	24 (27)	4 (21)	7 (37)
Progressive disease	1 (2)	3 (5)	2 (2)	0	0	0
Could not be evaluated	2 (4)‡	2 (4)‡	2 (2)	2 (2)	0	1 (5)
Duration of response						
No. of patients with objective response	38	34	64	59§	15	11
Data censored — no. (%)	32 (84)	25 (74)	60 (94)	56 (95)	9 (60)	8 (73)
Median (95% CI) — mo	NE (19.1–NE)	NE (18.4–NE)	22.0 (NE–NE)¶	22.0 (NE–NE)¶	18.4 (7.6–NE)	NE (9.5–NE)
Median follow-up — mo	14.1	14.8	7.8	8.0	17.5	17.5
Progression-free survival						
Data censored — no. (%)	42 (76)	33 (60)	80 (91)	82 (93)	11 (58)	12 (63)
Median (95% CI) — mo	NE (24.4–NE)	27.4 (13.7–NE)	23.6 (NE–NE)¶	23.6 (23.6–NE)¶	20.1 (9.4–NE)	NE (10.0–NE)
Median follow-up — mo	16.7	16.7	11.1	11.1	13.7	19.3
Prevalence at 1 yr (95% CI) — %	82 (69–90)	68 (54–79)	92 (82–97)	95 (86–98)	64 (37–82)	61 (33–81)

Wirth LJ, et al. N Engl J Med 2020;383:825-835

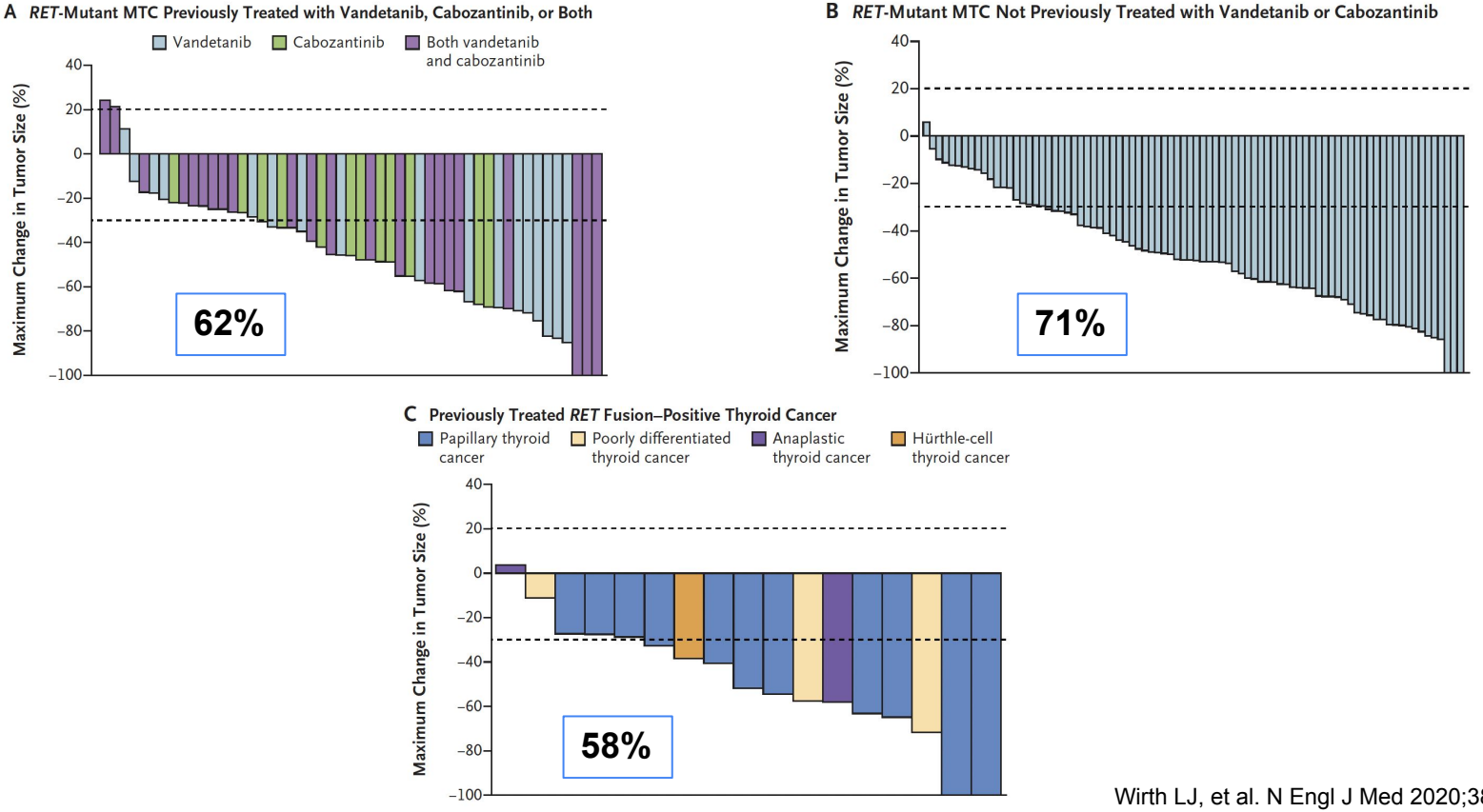
Table 2. Efficacy.*

Response	*RET*-Mutant MTC Previously Treated		*RET*-Mutant MTC Not Previously Treated		Previously Treated *RET* Fusion–Positive Thyroid Cancer	
	Independent Review (N=55)	Investigator Assessment (N=55)	Independent Review (N=88)	Investigator Assessment (N=88)	Independent Review (N=19)	Investigator Assessment (N=19)
Objective response — % (95% CI)	69 (55–81)	62 (48–75)	73 (62–82)	71 (60–80)	79 (54–94)	58 (34–80)
Progression-free survival						
Data censored — no. (%)	42 (76)	33 (60)	80 (91)	82 (93)	11 (58)	12 (63)
Median (95% CI) — mo	NE (24.4–NE)	27.4 (13.7–NE)	23.6 (NE–NE)¶	23.6 (23.6–NE)¶	20.1 (9.4–NE)	NE (10.0–NE)
Median follow-up — mo	16.7	16.7	11.1	11.1	13.7	19.3
Prevalence at 1 yr (95% CI) — %	82 (69–90)	68 (54–79)	92 (82–97)	95 (86–98)	64 (37–82)	61 (33–81)

	RET-mutant MTC Previously treated		RET-mutant MTC Not Previously treated		RET fusion-positive Previously treated	
N	55		88		19	
	Independent	Investigator	Independent	Investigator	Independent	Investigator
ORR (%)	69	62	73	71	79	58
1y-PFS (%)	82	68	92	95	64	61

Wirth LJ, et al. N Engl J Med 2020;383:825-835

Selpercatinib in RET-driven thyroid cancer – ORR

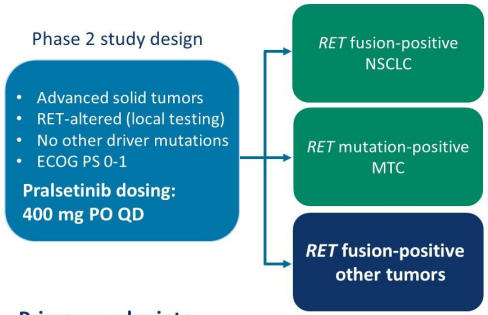


Wirth LJ, et al. N Engl J Med 2020;383:825-835

Pralsetinib for patients with advanced or metastatic *RET*-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study

Vivek Subbiah, Mimi I Hu*, Lori J Wirth, Martin Schuler, Aaron S Mansfield, Giuseppe Curigliano, Marcia S Brose, Viola W Zhu, Sophie Leboulleux, Daniel W Bowles, Christina S Baik, Douglas Adkins, Bhumsuk Keam, Ignacio Matos, Elena Garralda, Justin F Gainor, Gilberto Lopes, Chia-Chi Lin, Yann Godbert, Debashis Sarker, Stephen G Miller, Corinne Clifford, Hui Zhang, Christopher D Turner, Matthew H Taylor*

Pralsetinib Phase 1/2 ARROW



Primary endpoints

- **Centrally reviewed ORR per RECIST v1.1**
- **Safety**

Summary of tumour response to pralsetinib 400 mg*

	RET-mutant medullary thyroid cancer group		RET fusion-positive thyroid cancer group
	Previous cabozantinib or vandetanib, or both, treatment group (n=55)	No previous systemic treatment group (n=21)	All (n=9)
Overall response rate	33 (60%); (46–73)	15 (71%); (48–89)	8 (89%); (52–100)
Best overall response			
Complete response	1 (2%)	1 (5%)	0
Partial response	32 (58%)	14 (67%)	8 (89%)
Stable disease	18 (33%)	6 (29%)	1 (11%)
Progressive disease	2 (4%)	0	0
Disease control rate†	51 (93%); (82–98)	21 (100%); (84–100)	9 (100%); (66–100)
Clinical benefit rate‡	44 (80); (67–90)	21 (100%); (84–100)	8 (89%); (52–100)
Median time to first response, § months	3·7 (IQR 1·9–5·6)	5·6 (IQR 3·5–9·2)	1·9 (IQR 1·8–2·8)
Median duration of response, § months	NR (15·1–NE)	NR (NE–NE)	NR (NE–NE)
6 months	96% (90–100)	93% (81–100)	100% (100–100)
12 months	92% (82–100)	84% (63–100)	86% (60–100)

Subbiah V, et al. Lancet Diabetes Endocrinol 2021 Aug;9(8):491-501

Pralsetinib for patients with advanced or metastatic *RET*-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study

Vivek Subbiah, Mimi I Hu*, Lori J Wirth, Martin Schuler, Aaron S Mansfield, Giuseppe Curigliano, Marcia S Brose, Viola W Zhu, Sophie Leboulleux, Daniel W Bowles, Christina S Baik, Douglas Adkins, Bhumsuk Keam, Ignacio Matos, Elena Garralda, Justin F Gainor, Gilberto Lopes, Chia-Chi Lin, Yann Godbert, Debashis Sarker, Stephen G Miller, Corinne Clifford, Hui Zhang, Christopher D Turner, Matthew H Taylor*

Pralsetinib Phase 1/2 ARROW

	RET-mutant MTC Previously treated	RET-mutant MTC Not Previously treated	RET fusion-positive
N	55	21	9
ORR (%)	60	71	89
1y-PFS (%)	73	78	80

Summary of tumour response to pralsetinib 400 mg*

	RET-mutant medullary thyroid cancer group		RET fusion-positive thyroid cancer group
	Previous cabozantinib or vandetanib, or both, treatment group (n=55)	No previous systemic treatment group (n=21)	All (n=9)
		15 (71%); (48–89)	8 (89%); (52–100)
		1 (5%)	0
		14 (67%)	8 (89%)
		6 (29%)	1 (11%)
		0	0
		21 (100%); (84–100)	9 (100%); (66–100)
		21 (100%); (84–100)	8 (89%); (52–100)
		5·6 (IQR 3·5–9·2)	1·9 (IQR 1·8–2·8)
		NR (NE–NE)	NR (NE–NE)
response, § months			
6 months	96% (90–100)	93% (81–100)	100% (100–100)
12 months	92% (82–100)	84% (63–100)	86% (60–100)

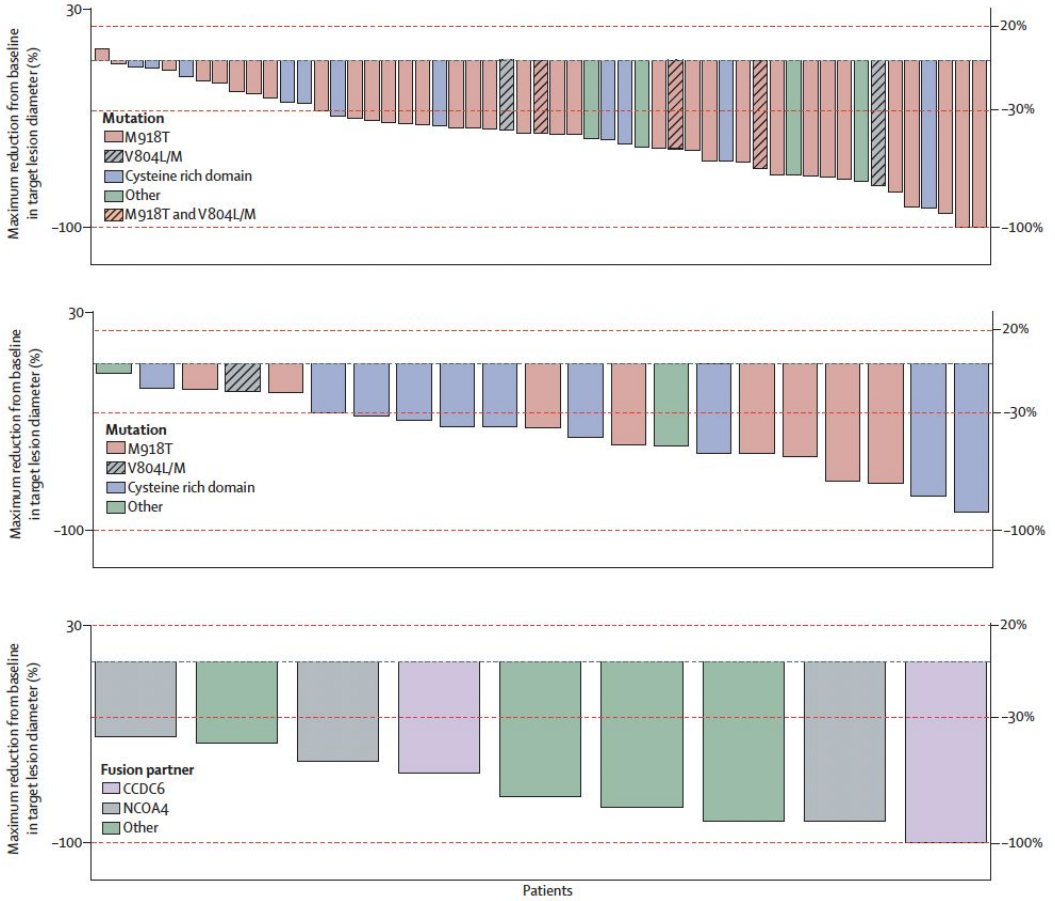
Subbiah V, et al. Lancet Diabetes Endocrinol 2021 Aug;9(8):491-501

Pralsetinib – ARROW trial

RET-mutant MTC previously treated with vandetanib, cabozantinib, or both □ **60%**

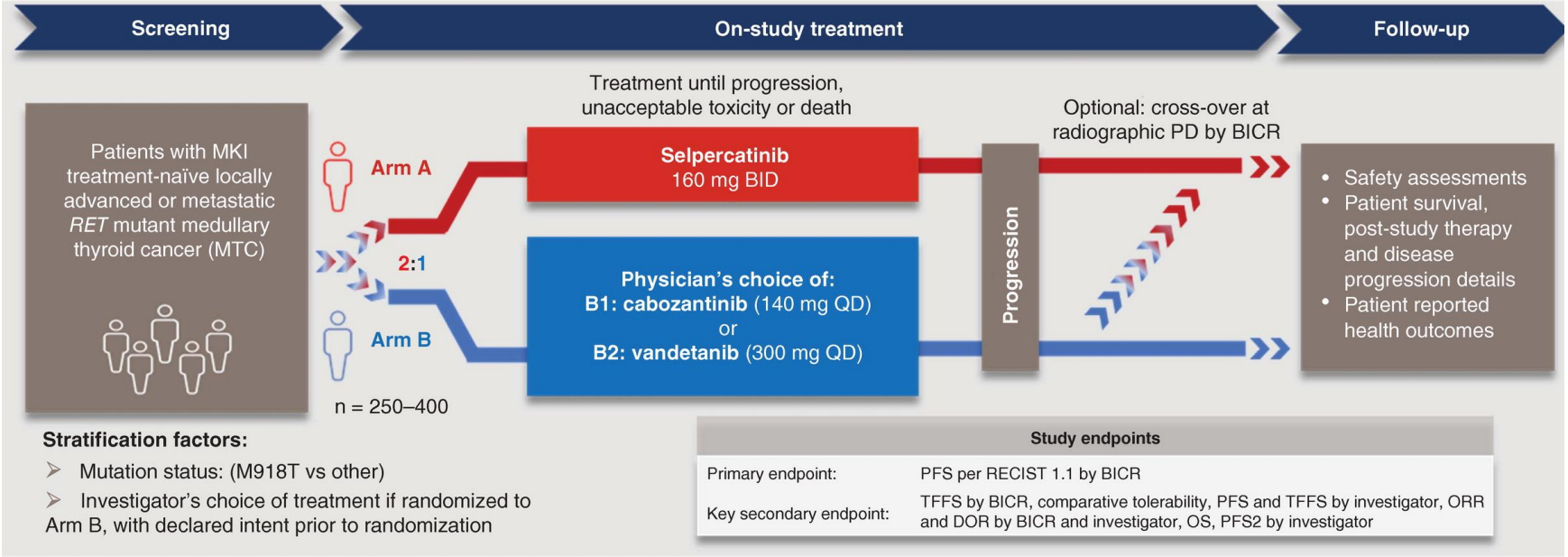
RET-mutant MTC not previously treated □ **71%**

RET fusion-positive thyroid cancer □ **89%**



Subbiah V, et al. Lancet Diabetes Endocrinol 2021 Aug;9(8):491-501

LIBRETTO-531: a phase III study of selpercatinib in multikinase inhibitor-naïve *RET*-mutant medullary thyroid cancer



Wirth LJ, et al. Future Oncol 2022 Sep;18(28):3143-3150

Phase III trials for selective RET inhibitors

Selpercatinib

LIBRETTO-531 (NCT04211337)

N = 400

Feb 2021

Selpercatinib 160 mg/12h
vs.
Cabozantinib/Vandetanib

1ry endpoint: PFS (BICR)
TTFS, ORR, DoR, OS

1st line
PD confirmed (14 m) by RECIST

Pralsetinib

AcceleRET-MTC (NCT04760288)

N = 198

Apr 2021

Pralsetinib 400 mg/24h
vs.
Cabozantinib/Vandetanib

1ry endpoint: PFS
TTF, ORR, OS

1st line
PD confirmed (14m) by RECIST +
Calcitonin/CEA doubling time <24m

Wirth LJ, et al. Future Oncol 2022 Sep;18(28):3143-3150

RET – Mechanisms of resistance

TABLE 1. Mechanisms of Acquired Resistance to Multikinase Inhibitors and Selective RET Inhibitors

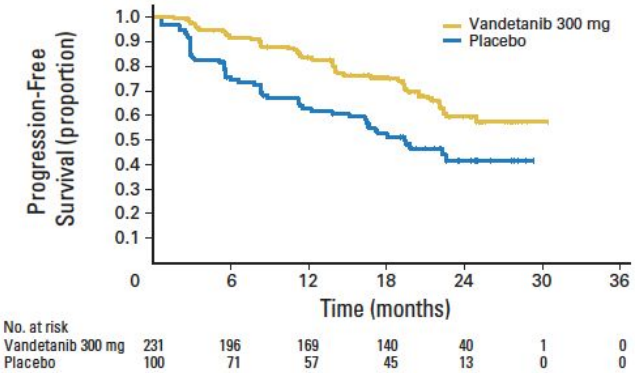
Mechanism	Alteration/Pathway	Source	Resistant to	Sensitive to
Secondary RET alterations	RET S904F	Patient sample	Vandetanib	—
	RET I788N	Preclinical model	AD80, cabozantinib	Ponatinib
	RET V804L/M	Preclinical model	Cabozantinib, vandetanib	BLU-667, LOXO-292
		Patient sample		
	RET G810A	Preclinical model	Vandetanib	Ponatinib, lenvatinib
	RET G810S and G810R	Preclinical model	BLU-667, LOXO-292	TPX-0046
Acquired non-RET alterations	MDM2 amplification	Patient sample	Cabozantinib	AMG232, RG7388; AMG232 + cabozantinib (all preclinical)
	NRAS Q61K	Preclinical model	Ponatinib	trametinib
Activation of bypass signaling	Activation of MAPK	Preclinical model	AD80	AD80 + trametinib
	Activation of EGFR	Preclinical model	Sunitinib, E7080, vandetanib (partial), sorafenib (partial)	Gefitinib or cetuximab + sunitinib, E7080, vandetanib, or sorafenib
	Activation of EGFR and AXL	Preclinical model	Ponatinib, cabozantinib, alectinib	Afatinib, gefitinib; afatinib + cabozantinib or foretinib

New RET inhibitors: BOS172738, TPX-0046, TAS0953/HM06

Subbiah V, et al. J Clin Oncol 2020 Apr 10;38(11):1209-1221

Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial

Samuel A. Wells Jr, Bruce G. Robinson, Robert F. Gagel, Henning Dralle, James A. Fagin, Massimo Santoro, Eric Baudin, Rossella Elisei, Barbara Jarzab, James R. Vasselli, Jessica Read, Peter Langmuir, Anderson J. Ryan, and Martin J. Schlumberger



sanofi

Comunicación Directa para los Profesionales Sanitarios

Caprelsa® (vandetanib): Restricción de indicación

20 de enero de 2023

Estimado profesional sanitario,

Sanofi, de acuerdo con la Agencia Europea de Medicamentos (EMA) y la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) desea informarle de lo siguiente:

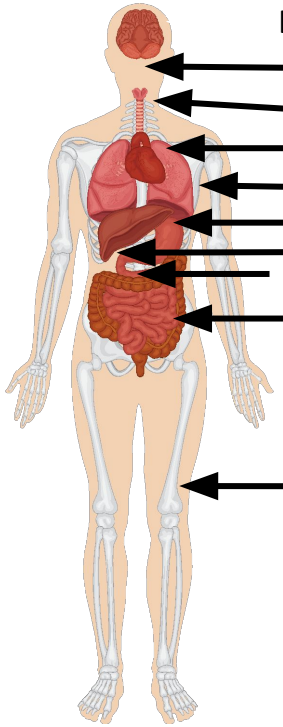
Resumen

- **Vandetanib no debe administrarse a pacientes en los que se desconozca el estado de la mutación del oncogén reorganizado durante la transfección (RET) o sea negativa.**
- **La restricción de la indicación se basa en los datos del estudio aleatorizado D4500C00058, y el estudio observacional OBS14778, que muestran una actividad insuficiente de vandetanib en pacientes sin mutaciones de RET identificadas.**
- **Antes de iniciar el tratamiento con vandetanib, debe determinarse la presencia de una mutación del gen RET mediante una prueba validada.**

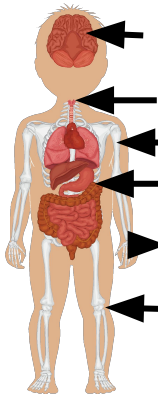
Wells SA, et al. J Clin Oncol 2012;30:134-141

NTRK

NTRK Fusions Are Rare Events: 0.27% Across >11,000 Patients With Tumors of All Types



Brain cancers (glioma, GBM, astrocytoma)
Salivary cancer (MASC)
Thyroid cancer
Lung cancer
Secretory breast cancer
Pancreatic
Cholangiocarcinoma
GIST
Colon
Melanoma
Sarcoma (multiple subtypes)



Gliomas
Thyroid cancer
Infantile fibrosarcoma
Congenital mesoblastic nephroma
Spitz nevi
Sarcoma (multiple subtypes)

Cancers with <5% TRK fusion
Common cancer with 5%-25% TRK fusions
Rare cancer with high incidence of TRK fusions (>90%)

Slide credit: clinicaloptions.com

Cocco E, et al. Nat Rev Clin Oncol 2018 Dec;15(12):731-747. Gatalica Z, et al. AACR-NCI-EORTC 2017. Abstr A047.

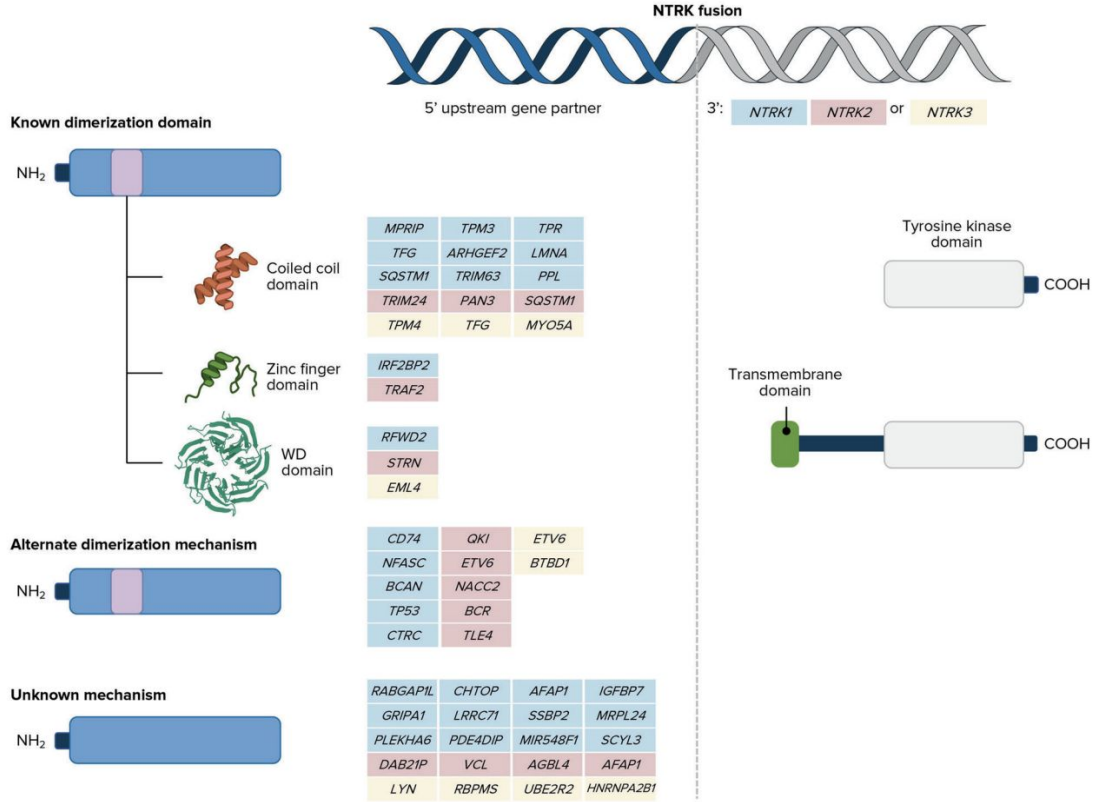


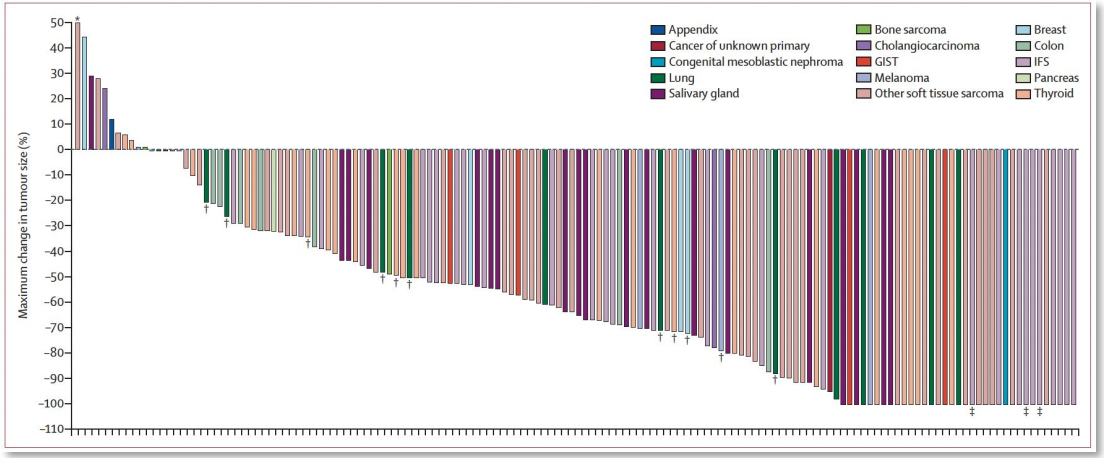
Table 1. Frequency of NTRK fusions in patients with cancer[16–18].

Histology	Frequency, %
Overall	0.28
Secretory breast carcinoma	92.87
Infantile fibrosarcoma	90.56
Secretory salivary gland cancer	79.68
Pleomorphic adenoma	50.47
Papillary thyroid carcinoma, pediatric	25.93
Differentiated thyroid cancer, pediatric	22.22
Inflammatory myofibroblastic tumor	17.7
Salivary gland carcinoma	5.08–5.29
Thyroid cancer	2.22–2.28
Sarcoma	0.68–1.17
Glioblastoma multiforme	0.62
Glioma/neuroepithelial tumor	0.55
Appendiceal adenocarcinoma	0.48–0.57
Melanoma	0.36–0.54
Biliary tract cancer	0.36
Cervical carcinoma	0.36
Colorectal cancer	0.26–0.35
Unknown primary	0.31
Neuroendocrine tumors	0.26–0.31
Pancreatic cancer	0.30–0.34
Cholangiocarcinoma	0.25
Lung adenocarcinoma	0.16–0.23
Invasive breast carcinoma[a]	0.08–0.13

Hechtman JF. Modern Pathology 2022;35:298-305

Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials

David S Hong, Steven G DuBois, Shivaani Kummar, Anna F Farago, Catherine M Albert, Kristoffer S Rohrberg, Cornelis M van Tilburg, Ramamoorthy Nagasubramanian, Jordan D Berlin, Noah Federman, Leo Mascarenhas, Birgit Geoerger, Afshin Dowlati, Alberto S Pappo, Stefan Bielack, François Doz, Ray McDermott, Jyoti D Patel, Russell J Schilder, Makoto Tahara, Stefan M Pfister, Olaf Witt, Marc Ladanyi, Erin R Rudzinski, Shivani Nanda, Barrett H Childs, Theodore W Laetsch, David M Hyman, Alexander Drilon**



	Patients	Patients with response	Median duration of response, months*
Overall	153	121 (79%, 72–85)	35·2 (22·8–NE)
Soft tissue sarcoma			
Infantile fibrosarcoma	28	27 (96%, 82–100)	NE (NE–NE)
Gastrointestinal stromal tumour	4	4 (100%, 40–100)	26·3 (7·6–26·3)
Other	36	29 (81%, 64–92)	NE (10·1–NE)
Thyroid	24	19 (79%, 58–93)	NE (14·8–NE)
Salivary gland	20	18 (90%, 68–99)	35·2 (13·3–NE)
Lung	12	9 (75%, 43–95)	NE (NE–NE)
Colon	8	4 (50%, 16–84)	3·7 (3·7–NE)
Melanoma	7	3 (43%, 10–82)	NE (3·7–NE)
Breast	4	3 (75%, 19–99)	NE (NE–NE)
Bone sarcoma	2	1 (50%, 1–99)	7·7 (NE–NE)
Cholangiocarcinoma	2	1 (50%, 1–99)	7·3 (NE–NE)
Pancreas	2	1 (50%, 1–99)	3·5 (NE–NE)
Appendix	1	0 (NC)	..
Congenital mesoblastic nephroma	1	1 (100%, 3–100)	NE (NE–NE)
Hepatocellular	1	0 (NC)	..
Unknown primary	1	1 (100%, 3–100)	NE (NE–NE)

Data are n, n (%, 95% CI), or median (95% CI). NC=not calculable. NE=not estimable. *In patients with confirmed responses (n=108).

Table 3: Proportion of patients with response and duration of responses by tumour type according to investigator assessment

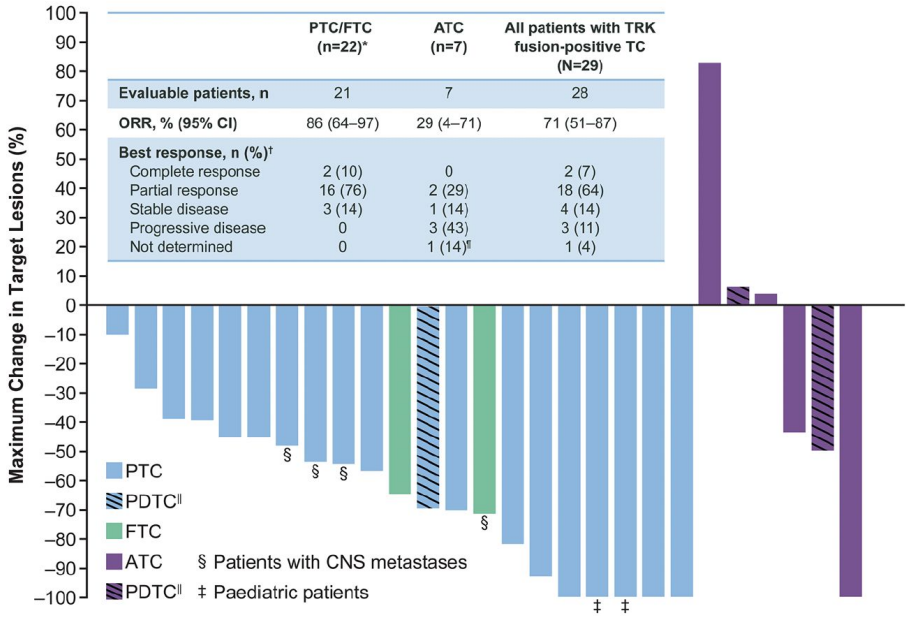
Hong DS, et al. Lancet Oncol 2020;21:531-540

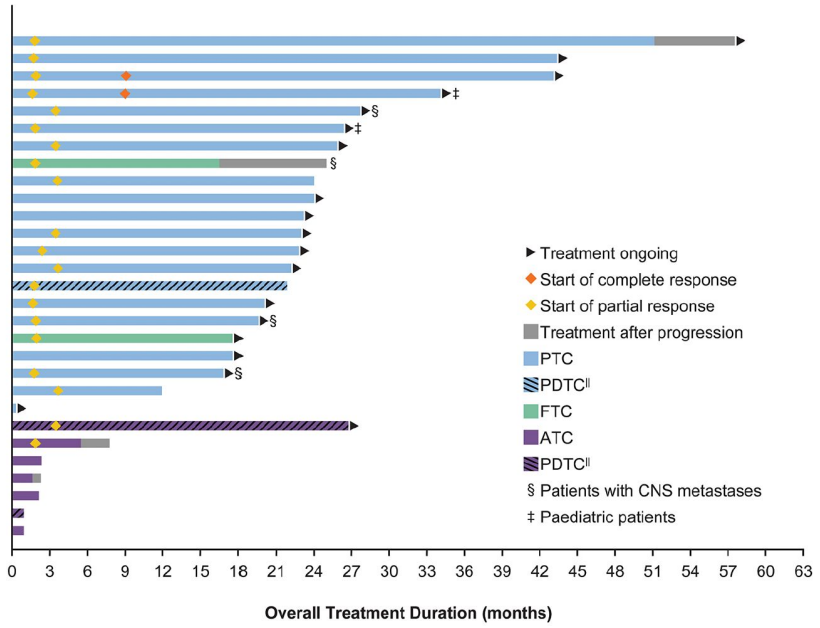
Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma

Steven G Waguespack[1], Alexander Drilon[2,3], Jessica J Lin[4,5], Marcia S Brose[6], Ray McDermott[7], Mohammed Almubarak[8], Jessica Bauman[9], Michela Casanova[10], Anuradha Krishnamurthy[11], Shivaani Kummar[12,†], Serge Leyvraz[13], Do-Youn Oh[14], Keunchil Park[15], Davendra Sohal[16], Eric Sherman[2], Ricarda Norenberg[17], Josh D Silvertown[18], Nicoletta Brega[19], David S Hong[1] and Maria E Cabanillas[1]

24-month DoR: 81%,
24-month PFS: 69%
24-month OS: 76%

	PTC/FTC (n=22)*	ATC (n=7)	All patients with TRK fusion-positive TC (N=29)
Evaluable patients, n	21	7	28
ORR, % (95% CI)	86 (64–97)	29 (4–71)	71 (51–87)
Best response, n (%)†			
Complete response	2 (10)	0	2 (7)
Partial response	16 (76)	2 (29)	18 (64)
Stable disease	3 (14)	1 (14)	4 (14)
Progressive disease	0	3 (43)	3 (11)
Not determined	0	1 (14)¶	1 (4)





Waguespack SG, et al. Eur J Endocrinol 2022 Apr 29;186(6):631-643

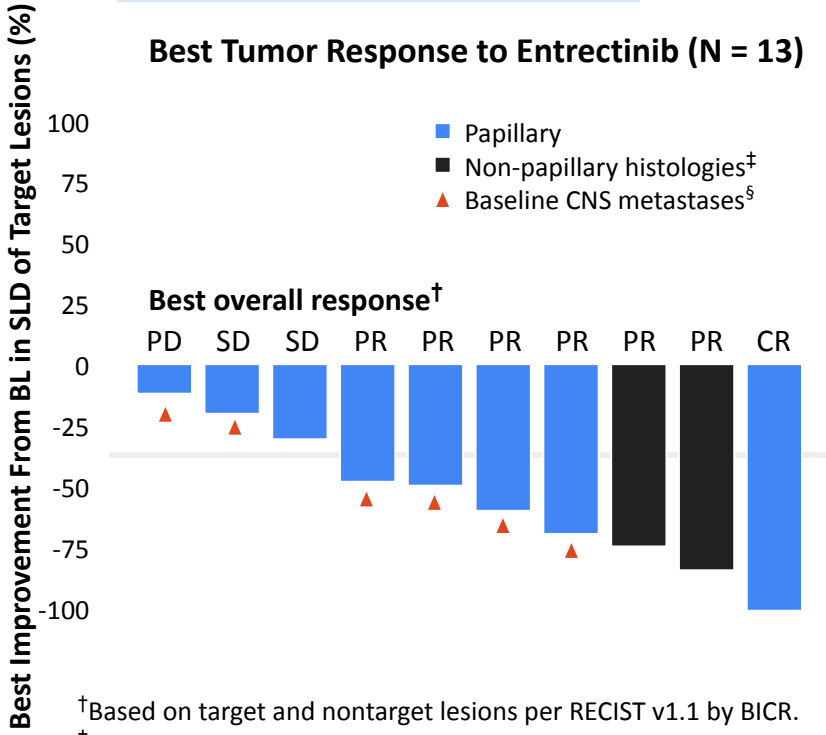
Entrectinib in Thyroid Carcinoma

- 13 patients with *NTRK* fusion–positive thyroid cancer from STARTRK-2
  - 31% had CNS mets at baseline
  - 77% papillary thyroid cancer
  - 69% *NTRK3*, 31% *NTRK1*

Outcome, n (%)	PTC (n = 10)	Nonpapillary* (n = 3)	All (N = 13)
ORR, % (95% CI)	50 (18.7-81.3)	67 (9.4-99.2)	54 (25.1-80.8)
▪ CR	1 (10)	0	1 (8)
▪ PR	4 (40)	2 (67)	6 (46)
▪ SD	2 (20)	0	2 (15)
▪ PD	1 (10)	0	1 (8)
▪ Non-CR/non-PR	0	1 (33)	1 (8)

RECIST v1.1 by BICR. *n = 1 each: thyroid cancer, ATC, MASC in thyroid.

Median DoR: 13.2 mo (7.9-NE)
Median PFS: 19.9 mo (6.5-33.8)
Median OS: 19.9 mo (14.5–NE)



†Based on target and nontarget lesions per RECIST v1.1 by BICR.
‡n = 1 each: thyroid cancer, ATC, MASC in thyroid.
§ By investigator.

Bowles DW, et al. 44th ETA Meeting, 2022. Abstr OP-03-14

IMMUNOTHERAPY

Immunotherapy in thyroid cancer

	Drug	n	ORR	PFS
KEYNOTE-028	Pembrolizumab	22	9%	6.8 mo
Dana Farber	Nivolumab + Ipilimumab	32 (DTC) 10 (ATC)	9% (DTC) 30% (ATC)	NA
ITOG	Lenvatinib + Pembrolizumab	28	64%	NR
PDR001	Spartalizumab	42 (ATC)	19%	1-y: 17-22%
DUTHY	Durvalumab+ Tremelimumab	37 (DTC) 19 (MTC) 12 (ATC)	8% (DTC) 16% (MTC) 33% (ATC)	5 mo

Mehnert JM, et al. BMC Cancer 2019 Mar 4;19(1):196. Lorch JH, et al. J Clin Oncol 38: 2020 (suppl; abstr 6513). Haugen B, et al. J Clin Oncol 2020;38:(suppl; abstr 6512). Capdevila J, et al. J Clin Oncol 2020;38:2620-2627. Capdevila J, et al.

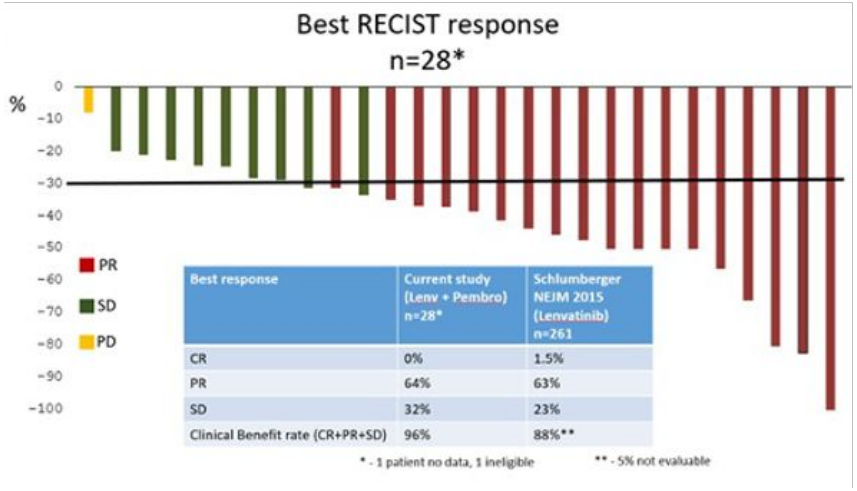
Lenvatinib plus Pembrolizumab Combination Therapy in Patients with Radioiodine-Refractory (RAIR), Progressive Differentiated Thyroid Cancer (DTC): Results of a Multicenter Phase II International Thyroid Oncology Group Trial

Bryan R Haugen[1], Jena D French[1], Francis P Worden[2], Bhavana Konda[3], Eric J Sherman[4], Ramona Dadu[5], Andrew G Gianoukakis[6], Shaylene A McCue[7], Nathan Foster[7], Daniel W Bowles[1], Lori J Wirth[8]

[1]University of Colorado Anschutz Medical Campus, [2]University of Michigan Health, [3]Ohio State University James Comprehensive Cancer Center, [4]Memorial Sloan Kettering Cancer Center, [5]MD Anderson Cancer Center, [6]Harbor UCLA Medical Center, [7]ACCRU, [8]Massachusetts General Hospital

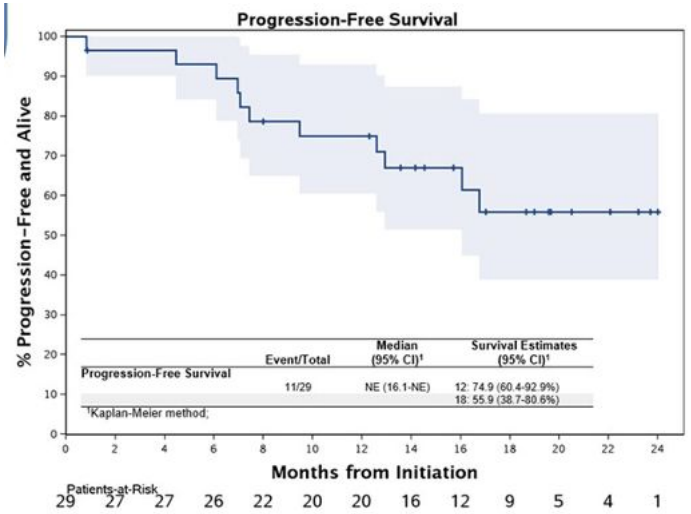
bryan.haugen@cuanschutz.edu

ITOG INTERNATIONAL THYROID ONCOLOGY GROUP



Best response	Current study (Lenv + Pembro) n=28*	Schlumberger NEJM 2015 (Lenvatinib) n=261
CR	0%	1.5%
PR	64%	63%
SD	32%	23%
Clinical Benefit rate (CR+PR+SD)	96%	88%**

* - 1 patient no data, 1 ineligible ** - 5% not evaluable



	Event/Total	Median (95% CI)[1]	Survival Estimates (95% CI)[1]
Progression-Free Survival	11/29	NE (16.1-NE)	12: 74.9 (60.4-92.9%) 18: 55.9 (38.7-80.6%)

[1]Kaplan-Meier method;

12-month PFS: 75%

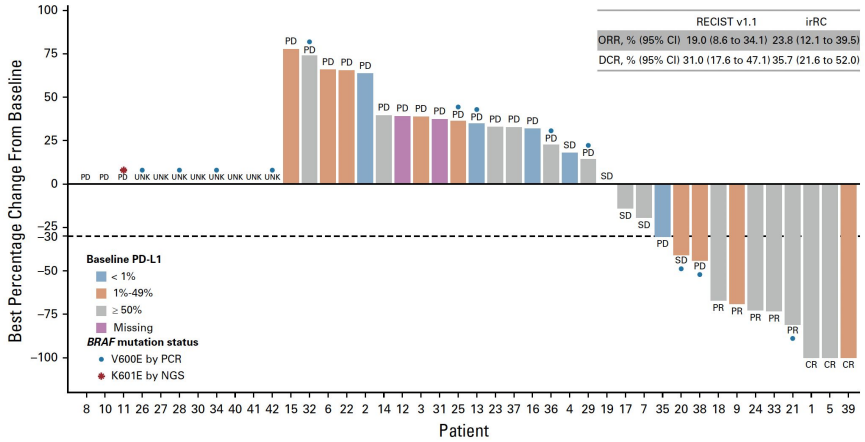
Haugen B, et al. J Clin Oncol 2020;38:(suppl; abstr 6512)

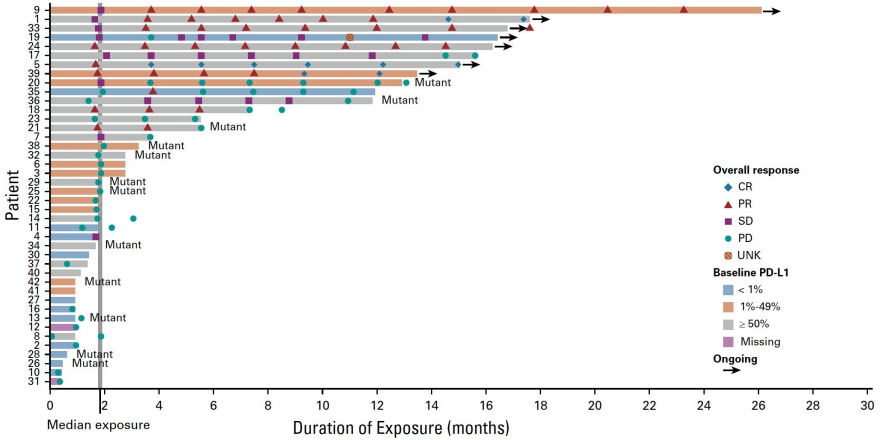
PD-1 Blockade in Anaplastic Thyroid Carcinoma

Jaume Capdevila, MD, PhD[1]; Lori J. Wirth, MD[2]; Thomas Ernst, MD[3]; Santiago Ponce Aix, MD[4]; Chia-Chi Lin, MD, PhD[5]; Rodryg Ramlau, MD, PhD[6]; Marcus O. Butler, MD[7]; Jean-Pierre Delord, MD, PhD[8]; Hans Gelderblom, MD, PhD[9]; Paolo A. Ascierto, MD[10]; Angelica Fasolo, MD[11]; Dagmar Führer, MD, PhD[12]; Marie Luise Hütter-Krönke, MD[13]; Patrick M. Forde, MBBCh[14]; Anna Wrona, MD, PhD[15]; Armando Santoro, MD[16]; Peter M. Sadow, MD, PhD[2]; Sebastian Szpakowski, PhD[17]; Hongqian Wu, PhD[18]; Geraldine Bostel, PhD[19]; Jason Faris, MD[17]; Scott Cameron, MD, PhD[17]; Andreea Varga, MD[20]; and Matthew Taylor, MD[21]

Phase I study: Spartalizumab
N=42
40% 1st line

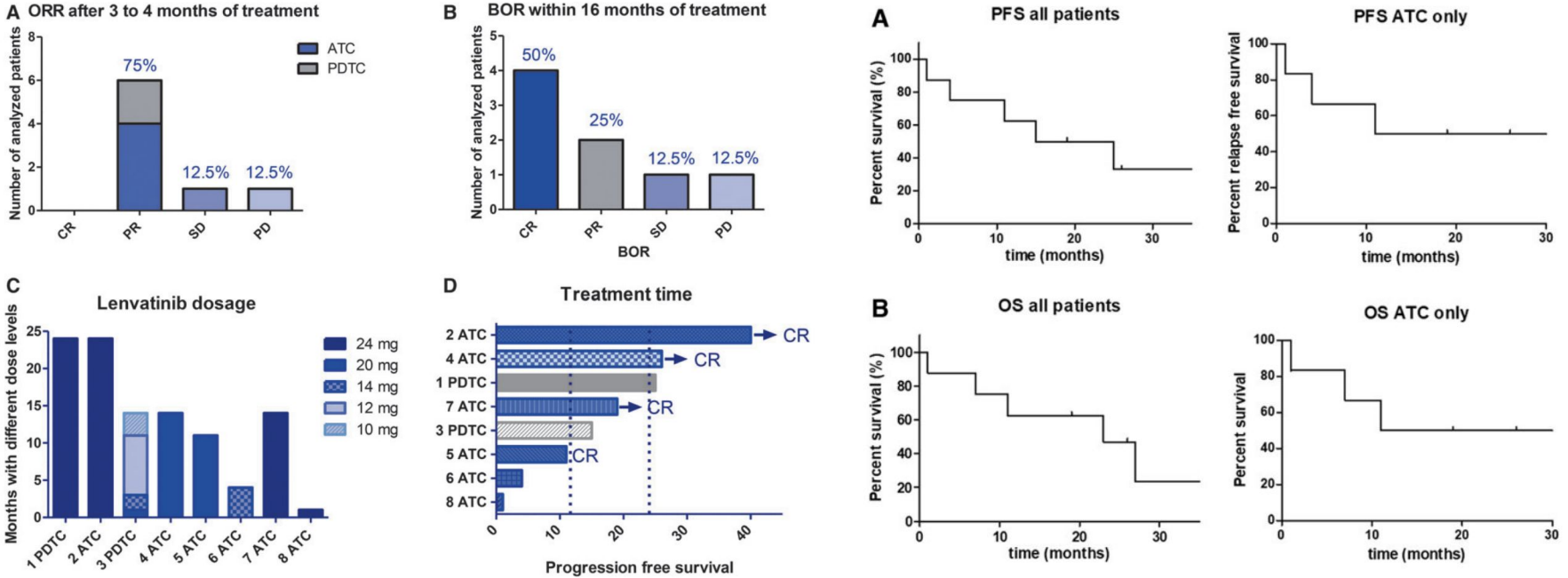
ORR: 19%
ORR PD-L1 > 50%: 35%
mPFS: 1.7 mo
1-y PFS: 17% (RECIST 1.1); 22% (irRC)
mOS: 5.9 mo
1-y OS PD-L1 > 50%: 52%





Capdevila J, et al. J Clin Oncol 2020;38:2620-2627

Combination of lenvatinib and pembrolizumab is an effective treatment option for anaplastic and poorly differentiated thyroid carcinoma

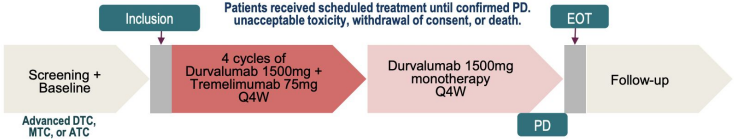


Dierks C, et al. Thyroid 2021 July;31(7):1076-1085

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

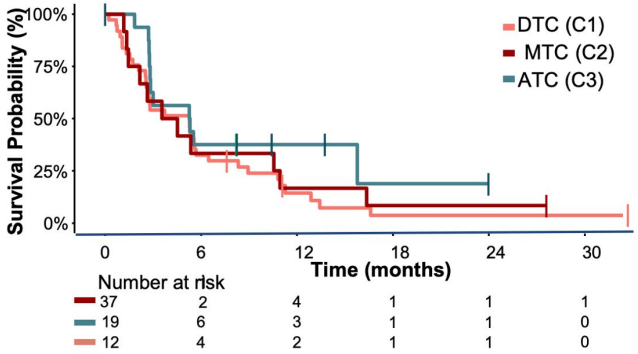
PARIS 2022 ESMO congress

DUTHY trial



EFFICACY ENDPOINTS: PFS

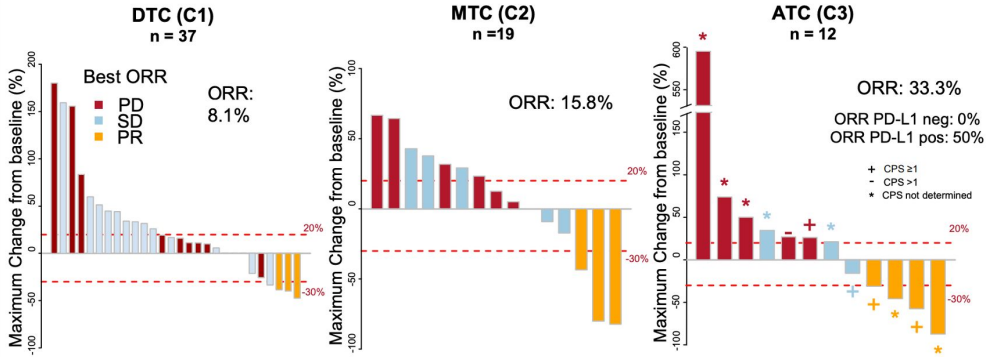
The median follow-up was 12.2 m (range: 0.2-34.5) / 16.8 m (range: 1.4-32.9) / 11.5 m (range: 1.5-29.9)



Cohort	6m PFS, % (95%CI)	Median PFS; m (95%CI)
DTC	32.4 (20.4-51.6)	5.3 (2.7-6.5)
MTC	37.5 (19.9-70.6)	5.3 (2.8-NR)
ATC	33.3 (15-74.2)	4 (2.2-NR)

NR: not reached

EFFICACY ENDPOINTS: ORR



Capdevila J, et al. Ann Oncol 2022;33 (suppl_7): S750-S757

MOLECULAR TESTING AND THERAPY: WHEN, HOW AND WHO

American Head and Neck Society Endocrine Surgery Section and International Thyroid Oncology Group consensus statement on mutational testing in thyroid cancer: Defining advanced thyroid cancer and its targeted treatment

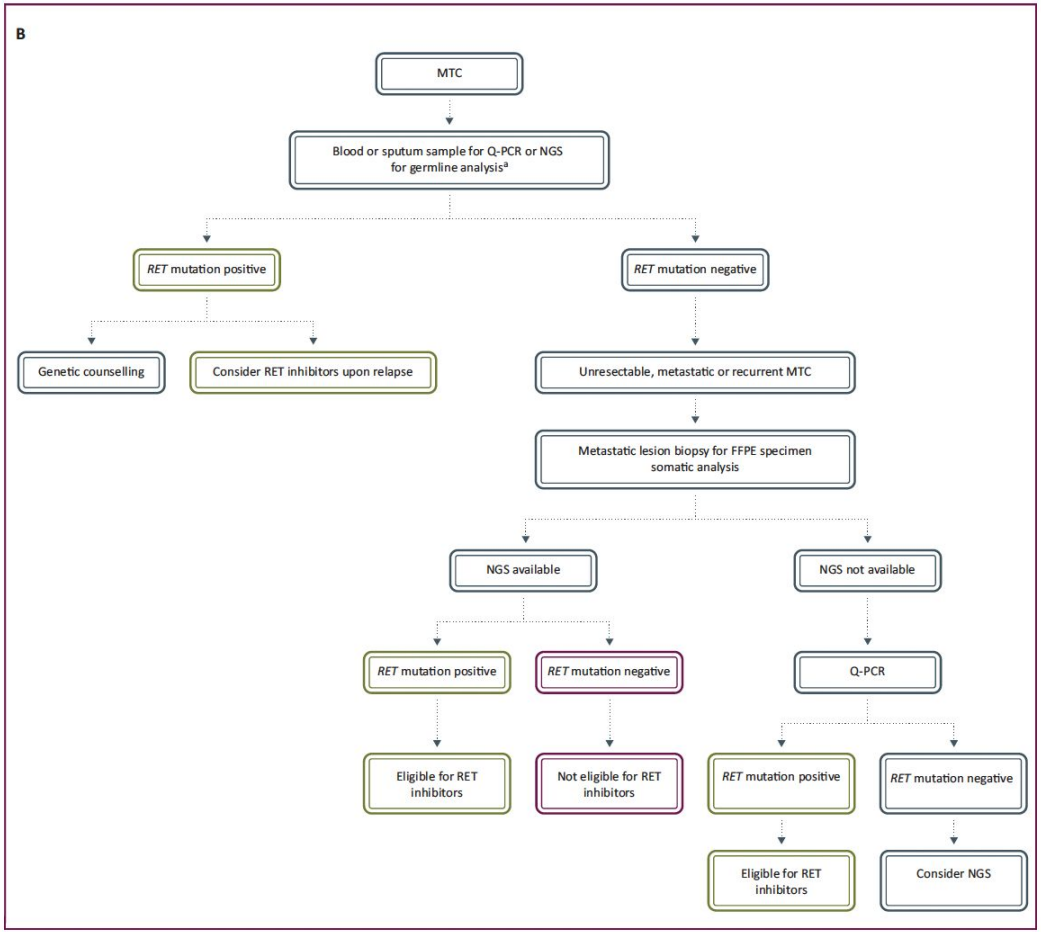
Obtain full molecular profile for any patient not expected to be cured by surgery / RAI and who might need systemic therapy

DTC/PDTC
Bulky, invasive, inoperable primary/locoregional disease
RAI nonavid/unresponsive
Structural volumetric doubling time <6 mo
Gross residual neck disease when XRT not appropriate or further surgery not feasible or should be delayed
Anatomically detectable recurrent disease
Other features that portend aggressive behavior at discretion of treating physician

ATC
All are stage IV and should be considered advanced even when resected completely

MTC
Biochemical or structural volumetric doubling time <6 mo
Bulky, invasive, inoperable primary/ locoregional disease
Anatomically detectable recurrent disease
Other aggressive features

Shonka DC, et al. Head Neck 2022 Jun;44(6):1277-1300



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

NCCN National Comprehensive Cancer Network®

All patients with MTC should have **germline testing.**

All patients with sporadic recurrent/persistent locoregional or metastatic MTC incurable by surgery should have **tumor somatic testing.**

- ~50% will have a somatic RET mutation.

If somatic RET mutation identified, **germline testing** for RET mutations also should be performed.

- 7% will have a germline RET mutation.

Belli C, et al. Ann Oncol 2021 Mar;32(3):337-350
NCCN Guidelines Thyroid Carcinoma. Version 3.2022. www.nccn.org

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ANNALS OF ONCOLOGY driving innovation in oncology

ESMO recommendations on the standard methods to detect *RET* fusions and mutations in daily practice and clinical research

C. Belli[1†], F. Penault-Llorca[2†], M. Ladanyi[3], N. Normanno[4], J.-Y. Scoazec[5,6], L. Lacroix[7,8,9], J. S. Reis-Filho[10], V. Subbiah[11], J. F. Gainor[12], V. Endris[13], M. Repetto[1,14], A. Drilon[15,16†], A. Scarpa[17], F. André[18], J.-Y. Douillard[19] & G. Curigliano[1,14*]

Table 1. Summary of main features, strengths and weaknesses of all available techniques to detect *RET* rearrangements

Method	Sensitivity	Specificity	Detection of partner	Detection of expression	Screening
IHC	Moderate[a]	Moderate[b]	No	Yes	No
FISH	High	High	No/Yes[c]	No	Rare circumstances
RT-PCR	Moderate/high[d]	High	Yes/No[e]	Yes	Rare circumstances
DNA-seq NGS	Moderate[f]	High/moderate[g]	Yes	No	Yes
RNA-seq NGS	High	High	Yes	Yes[h]	Yes

DNA-seq NGS, DNA sequencing by next-generation sequencing; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; RNA-seq NGS, RNA sequencing by next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction.

Belli C, et al. Ann Oncol 2021 Mar;32(3):337-350

JSCO—ESMO—ASCO—JSMO—TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or *NTRK* fusions

T. Yoshino[1*], G. Pentheroudakis[2], S. Mishima[1], M. J. Overman[3], K.-H. Yeh[4], E. Baba[5], Y. Naito[6], F. Calvo[7], A. Saxena[8], L.-T. Chen[9], M. Takeda[10], A. Cervantes[11], H. Taniguchi[1], K. Yoshida[12], Y. Kodera[13], Y. Kitagawa[14], J. Tabernero[15], H. Burris[16] & J.-Y. Douillard[17]

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CQ1: Should all patients with solid tumours be tested for *NTRK* fusion?

Recommendation CQ1-1. Patients ***with advanced (unresectable or metastatic)*** *solid tumours* ***without*** *actionable and* driver gene *mutations/****fusions/amplifications*** *should be tested for NTRK fusion.*
[LoE: V, GoR: B, ***LoA: A = 100%****]*

Recommendation CQ1-2. Patients with ***advanced (unresectable or metastatic)*** *solid tumours which are* ***highly likely to harbour NTRK fusions*** *should be tested for NTRK fusion, especially ETV6-NTRK3 fusion.*
[LoE: V, GoR: A, ***LoA: A = 100%****]*

Recommendation CQ1-3. Patients with ***advanced (unresectable or metastatic)*** *solid tumours other than above (CQ1-1 and 1-2) should be considered for testing for NTRK fusions.*
[LoE: V, GoR: A, ***LoA: A = 100%****]*

Recommendation CQ1-4. ***Patients with locally-advanced tumours with a high incidence of NTRK fusions should be tested when considering neoadjuvant therapy before resection.***
[LoE: V, ***GoR: B, LoA: A = 100%****]*

CQ2. When is the optimal timing for tests for *NTRK* fusion?

Recommendation CQ2. NTRK fusion ***testing*** *should be* ***considered*** *before or during the standard treatment of advanced solid tumours.*
[LoE: V, GoR: ***B, LoA: A = 100%****]*

CQ3. Which tests are recommended for determining *NTRK* fusions?

Recommendation CQ3-1. IHC (immunohistochemistry) is not recommended for confirming NTRK fusion. It may be used for screening to enrich for patients with NTRK fusions.
[LoE: V, GoR: B, ***LoA: A = 100%****]*

Recommendation CQ3-2. In situ hybridisation [ISH, e.g. fluorescence ISH (FISH)] for ETV6-NTRK3 fusion is recommended for patients with tumours which are highly likely to harbour NTRK fusions. ISH is not recommended for patients other than the above.
[LoE: V, GoR: B, ***LoA: A = 100%****]*

Recommendation CQ3-3. Reverse transcriptase (RT)-PCR for ETV6-NTRK3 fusion is recommended for patients with tumours which are highly likely to harbour NTRK fusions.
[LoE: V, GoR: B, ***LoA: A = 100%****]*

Recommendation CQ3-4. Next generation sequencing (NGS) which detects NTRK fusion is recommended for testing NTRK fusion.
[LoE: V, GoR: C, ***LoA: A = 100%****]*

CQ4. What is the appropriate biospecimen for testing for *NTRK* fusions?

Recommendation CQ4. Both fresh samples as well as archival tissue samples properly fixed and preserved are appropriate for testing.
[LoE: V, GoR: B, ***LoA: A = 100%****]*

Yoshino T, et al. Ann Oncol 2020 Jul;31(7):861-872

Molecular genotyping in refractory thyroid cancers: results of a European survey - 1750P

Christelle de la Fouchardière[1], Laura Fugazzola[2], Judith Taylor[3], Maria Luisa Appetecchia[4], Nicolas Besic[5], Alberto Bongiovanni[6], Camille Buffet[7], Giuseppe Costante[8], Stefano Gay[9], Enrique Grande[10], Ellen HW Kapiteijn[11], Jolanta Krajewska[12], Matthias Kroiss[13], Hans Morreau[11], Romana Netea-Maier[14], Robin Peters[15], Paula Soares[16], Gerasimos Sykiotis[17], Jean-Yves Blay[1], Laura Locati[18]

(1)Medical Oncology Department, Centre Léon Bérard, Lyon, France; (2)University of Milan, Italy; (3)Thyroid Cancer Alliance; (4)Regina Elena National Cancer Institute IFO IRCCS, Rome, Italy; (5)Onkoloskii Institut, Ljubljana, Slovenija.(6)IRCCS,Meldola, Italy; (7)Hôpital Pitié Salpêtrière, Paris, France; (8)Institut Jules Bordet, Belgium; (9)Policlinico San Martino, Genoa, Italy; (10)MD Anderson Cancer Center Madrid, Spain, (11)Leiden University Medical Center, The Netherlands; (12)Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland; (13)University of Würzburg, Germany; (14) Radboud University Medical Center, Nijmegen, The Netherlands; (15) Erasmus MC, Rotterdam, the Netherlands; (16) University of Porto, Porto, Portugal; (17) CHUV, Lausanne, Switzerland;; (18)Istituto Nazionale dei Tumori, Milan, Italy.

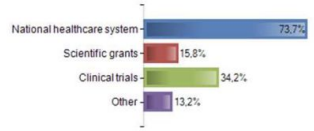
Background: The management of refractory thyroid cancers (TC) (radioiodine refractory thyroid cancer (RAIR-TC), metastatic medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC)) has recently changed with the arrival of new and effective treatments that target specific molecular abnormalities. However, differences in the ability to offer molecular somatic screening and targeted treatments exist and can lead to disparities in cancer care.

Methods: From Nov 18th 2020 to Jan 18th 2021, an online survey invitation was sent to EURACAN G6 Group, EORTC Endocrine Group and ETA members. It comprised 19 questions regarding country, medical practice modalities (medical specialty, institution type, involvement in aggressive TC management), molecular genotyping capacities, and reimbursement/funding and treatment access modalities.

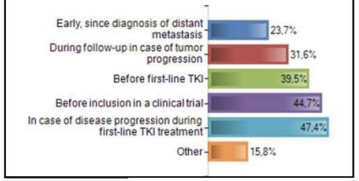
Results: A total of **86 practitioners** from **18 European Union countries** (n=83), **Switzerland** (n=2) and **Turkey** (n=1) responded. Most were endocrinologists (47.7%) and worked in academic centres (57.1%). Forty-seven of them (54.6%) declared being routinely involved in managing aggressive TC including 38/47 (80.9%) regularly prescribing somatic molecular genotyping. The preferred methods were tumor DNA-based techniques for gene mutations (89.8%) and gene fusions (64.4%), which were mainly funded by national healthcare systems (73.7%). Among those not prescribing molecular analyses, main reasons were lack of reimbursement (46.7%), lack of established workflow (46.7%) and lack of access to targeted therapies (40%). The most frequently searched molecular alterations were **BRAF mutations**, **RET and NTRK fusions** in RAIR-TC, **RET mutations** in MTC, and **BRAF mutations and NTRK fusions** in ATC. Access to selective inhibitors is mainly driven by clinical trials, with routine-access to therapies being available in only 40% of the institutions.

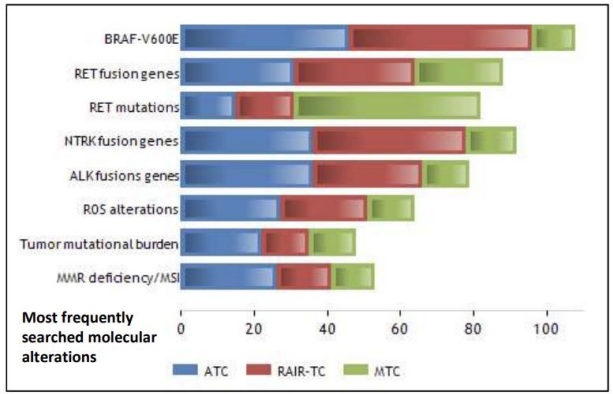
Repartition of genotyping prescriptions according to TC type

Financing source for tumor genotyping

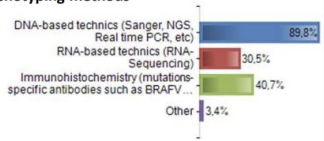


Prescription timing within disease course

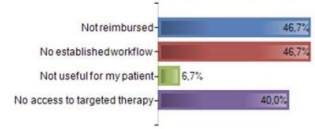




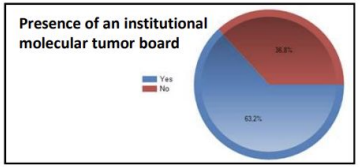
Genotyping methods



Reasons for not prescribing tumor genotyping



Presence of an institutional molecular tumor board



de la Fouchardière C, et al. Ann Oncol 2021; 32 (suppl_5): S1205-S1210

ID # 463

MOLTHY Project: A Spanish Observational Study For Molecular Characterization Of Thyroid Carcinoma

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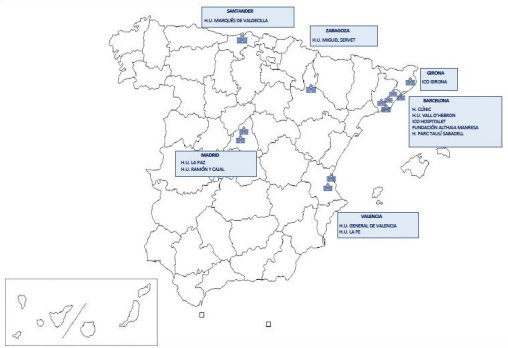
Background

- Thyroid cancer (TC) is the most frequent endocrine cancer.
- Treatment is generally based on surgery +/- radioactive iodine (RAI) and TSH suppression in differentiated TC (DTC), and surgery in medullary TC (MTC).
- Multiple kinase inhibitor drugs are considered the standard of care for advanced TC. New molecular-driven alterations therapies have emerged such as neurotrophic tyrosine kinase receptor (NTRK) and rearranged during transfection (RET) inhibitors.
- The availability of molecular profiling test at cancer centers provides precision medicine in clinical routine and new treatment opportunities.
- To date, there is no information of molecular alterations prevalence in Spain of patients with advanced MTC and RAI-Refractory (R) DTC. There is a need to define the optimal molecular testing strategy to identify actionable mutations.

Figure 1: Participating Medical Centers



Study design

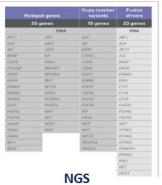
MOLTHY is a multicenter multidisciplinary translational project aiming to:

- Characterize the molecular profiling of advanced MTC and RAI-R DTC in a Spanish cohort,
- Identify potential molecular-driven alterations and the impact on survival, and
- Compare different molecular testing in a retrospective cohort of

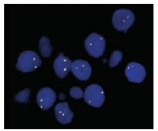
150 patients diagnosed of advanced RAI-R DTC and advanced MTC at the thyroid cancer units of 12 Spanish sites, belonging to both Spanish Cooperative groups TTCC and GETNE.

Demographic, clinicopathologic, survival data will be collected for two years. Surgical tumor samples (FFPE) will be analyzed at Hospital Clinic Barcelona for molecular profiling, including different diagnostic techniques:

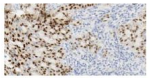
- **Oncomine focus assay** (Ion Torrent Platform-52-gene NGS panel to detect mutations, copy number alterations, gene rearrangements).
- **Fluorescence In Situ Hybridization (FISH):** To identify *RET*, *NTRK1* and *NTRK3* alterations.
- **Immunohistochemistry (IHC) staining** VENTANA pan-TRK (EPR17341) Assay to identify *NTRK* alteration.



NGS



FISH



IHC

A comparison of different molecular testing techniques will be explored, with the aim to propose a diagnostic decision-making in advanced TC, especially for *NTRK* and *RET* alterations. **(NCT04970134)**

Study progress

- Study enrollment started in June 2021 across **12** sites in Spain and it is expected to be completed in June 2023. Recruitment has been on hold during June-September 2022.
- There are currently **111** included patients.

Figure 2: Histological TC subtypes

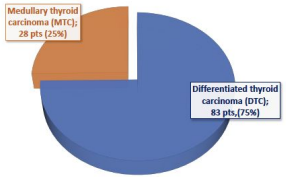
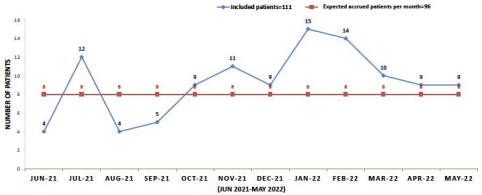


Figure 3: Recruitment plan



No conflict of interests
Roche Diagnostics has sponsored Ventana pan-TRK (EPR17341) kits

Contact: Neus Basté Rotllan. Hospital Clinic Barcelona, IDIBAPS, Spain
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CLINICAL PRACTICE GUIDELINES

Differentiated / poorly differentiated TC

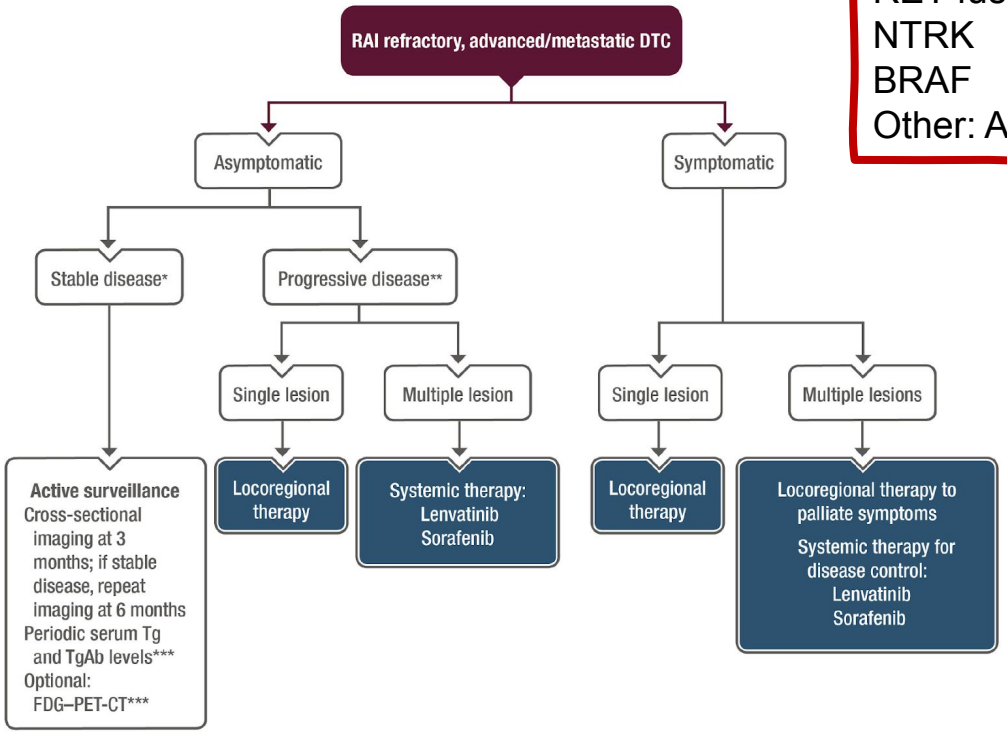
Management of advanced/metastatic disease

Recommendations for management of RAI-refractory, advanced/metastatic DTC patients

*A large tumour burden may warrant either a locoregional or systemic therapy

**As assessed by the RECIST v1.1

***The trend overtime of serum Tg or TgAb levels and the uptake at FDG—PET may predict disease progression and outcome



RET fusions
NTRK
BRAF
Other: Alk

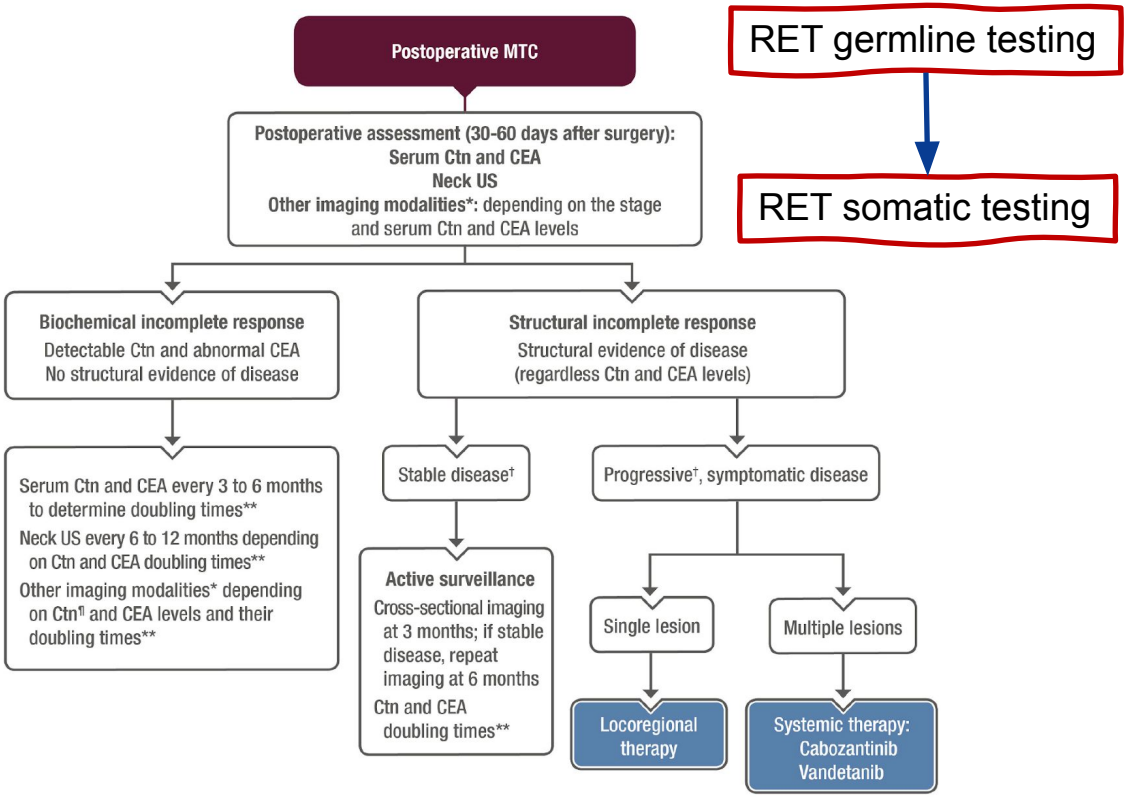
ESMO

CLINICAL PRACTICE GUIDELINES

Medullary Thyroid Cancer

Recommendations for postoperative MTC – incomplete response

*Multimodality imaging should be used to identify and to follow locoregional and/or distant metastases
**Serum Ctn and CEA doubling times are efficient tools for predicting tumour progression. Doubling times shorter than 24 months are associated with progressive disease
¶ Clinically relevant disease sites are rarely detected in patients with Ctn levels < 150 pg/mL
† Stable or progressive disease according to RECIST 1.1. In patients with stable disease, a large tumour burden may warrant either a locoregional or systemic therapy



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CLINICAL PRACTICE GUIDELINES

Anaplastic Thyroid Cancer

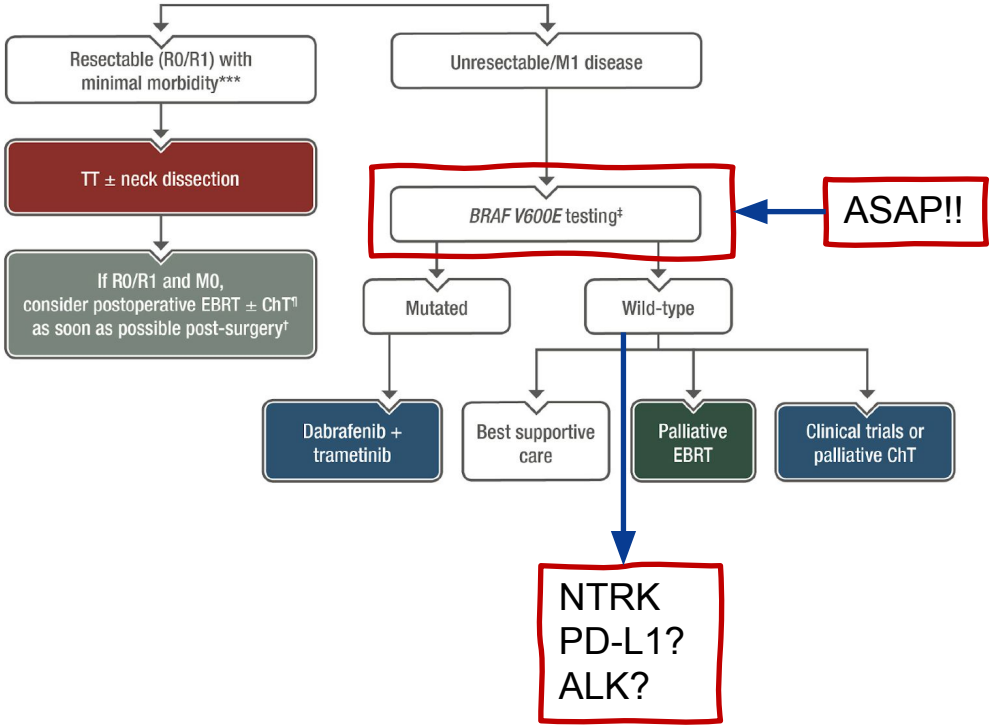
Recommendations for management of ATC patients - Treatment

***Laryngectomy not appropriate. Elective tracheostomy should be avoided

¶Concomitant ChT should be offered in patients who have good PS

†Preferably within 3 weeks of surgery. IMRT is the recommended approach

‡A next-generation sequencing analysis targeting cancer-associated genes is the preferred approach if available



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GENERAL SCENARIO

Histologic type (frequency, %)	Genetic alterations	Therapeutic options	Molecularly-driven options	Future options?
Papillary (80%)	BRAF: 40-60% RAS (NRAS): 10-20% **RET/PTC: 10-20%** **NTRK: <5%**	Lenvatinib Sorafenib Cabozantinib	*RET-driven:* Selpercatinib Pralsetinib *NTRK-driven:* Larotrectinib Entrectinib	BRAF inhibitors Redifferentiation IO-TKI combos
Follicular (14%)	RAS: 40-50% PAX-8/PPARγ: 30-35% PTEN: <10%			
Medullary (4%)	**RET (hereditary): 95%** **RET (sporadic): 50%** RAS (KRAS/HRAS):10%	~~Vandetanib~~ Cabozantinib	*RET-driven:* Selpercatinib Pralsetinib Vandetanib	Immunotherapy PRRT
Anaplastic (2%)	P53: 50-80% **BRAF: 20-40%** RAS: 20-40% **NTRK: <5%**	Limited Chemotherapy	*BRAF V600E-driven:* Dabrafenib-trametinib	Immunotherapy (PD-L1?)

MUCHAS GRACIAS

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