VIRTUAL 2020 ESMO congress

ONCO NOUVELLE-AQUITAINE
Réseau Régional de Cancérologie

BRIO BORDEAUX | Recherche Intégrée Oncologie

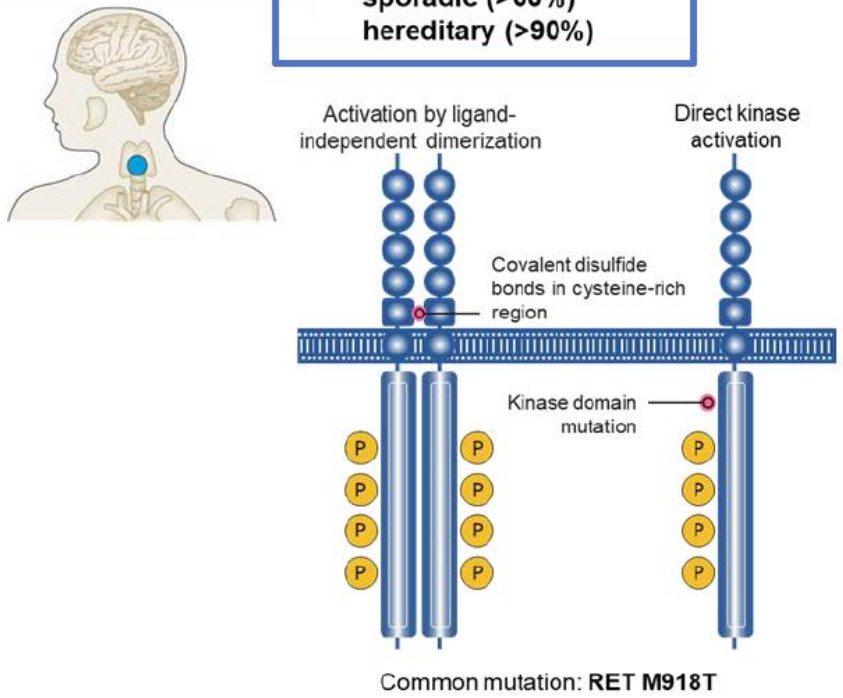
Thyroïde

Dr Godbert, Médecin nucléaire
Institut Bergonié, Bordeaux

RET is activated by two major mechanisms in thyroid cancer

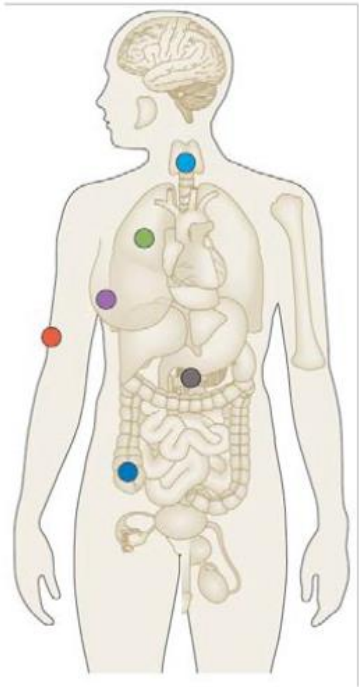
RET mutations

Medullary thyroid cancer
sporadic (>60%)
hereditary (>90%)

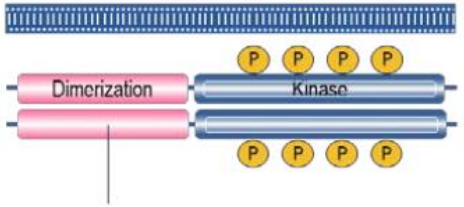


Common mutation: **RET M918T**

RET fusions



Non-small cell lung cancer (2%)
Thyroid cancers (10–20%)
Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

Anti-RET multikinase inhibitors (MKIs): approved for MTC and differentiated thyroid cancers but highly toxic; treatment options after failure of 1st MKI are limited

DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER

Preclinical and clinical activity, IC50, and efficacy of multikinase *versus* selective RET Inhibitors in MTC

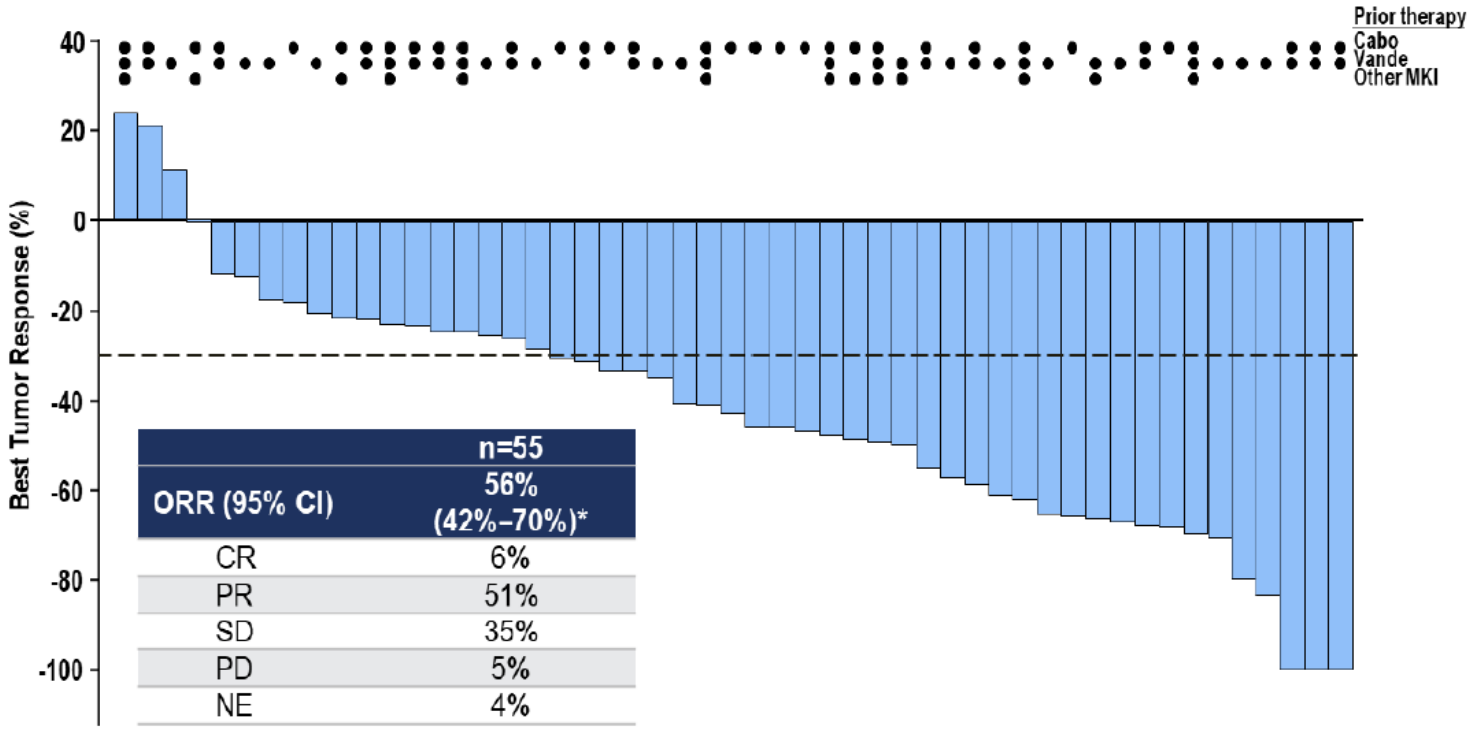
Drug	IC50, nM					
	RET					
	WT	M918T	V804L	V804M	CCDC6-RET	VEGFR2
Vandetanib	4	7	3,597	726	20	4
Cabozantinib	11	8	45	162	34	2
LOXO-292	0.4	0.7	-	0.8	-	100
BLU-667	0.4	0.4	0.3	0.4	0.4	35

ESMO

Subbiah V, *et al.* J Clin Oncol 2020;38:1-14.

DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER

LIBRETTO – 001: Activity of selpercatinib in RET-mutant MTC primary analysis set (N=55)



	n=55
ORR (95% CI)	56% (42%–70%)*
CR	6%
PR	51%
SD	35%
PD	5%
NE	4%

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.

Wirth L, *et al.* Ann Oncol 2019:30 (suppl_5):v933. Presented at ESMO; abstract LBA93; with permission from Dr L. Wirth. .

DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER

LIBRETTO – 001: Updated results from selpercatinib in RET-mutant MTC and RET fusion+ TC

	RET-mutant MTC				Previously-Treated *RET* Fusion+ Thyroid Cancer	
	Vandetanib and/or Cabozantinib Pretreated		Vandetanib and Cabozantinib Naïve			
	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 rate, % (95% CI)	69 (55–81)	62 (48–75)	73 (62–82)	71 (60–80)	79 (54–94)	58 (34–80)
Best response, n (%)						
Complete response	5 (9)	3 (6)	10 (11)	3 (3)	1 (5)	0
Partial response	33 (60)	31 (56)	54 (61)	59* (67)	14 (74)	11 (58)
Stable disease	14 (26)	16 (29)	20 (23)	24 (27)	4 (21)	7 (37)
Progressive disease	1 (2)	3 (6)	2 (2)	0	0	0
Not evaluable	2 (4)**	2 (4)**	2 (2)	2 (2)	0	1 (5)
Duration of Response						
Responders	38	34	64	59†	15	11
Censored, n (%)	32 (84)	25 (74)	60 (94)	56 (95)	9 (60)	8 (73)
Median, months (95% CI)	NE (19–NE)	NE (18–NE)	22‡ (NE–NE)	22‡ (NE–NE)	18 (8–NE)	NE (10–NE)
Median follow-up, months	14	15	8	8	18	18
Progression-free Survival						
Censored, n (%)	42 (76)	33 (60)	80 (91)	82 (93)	11 (58)	12 (63)
Median, months (95% CI)	NE (24–NE)	27 (14–NE)	24‡ (NE–NE)	24‡ (24–NE)	NE (10-NE)	20 (9–NE)
Median follow-up, months	17	17	11	11	14	19
1-year PFS rate, % (95% CI)	82 (69–90)	68 (54–79)	92 (82–97)	95 (86–99)	64 (33–81)	61 (37–82)

*Includes 3 patients with unconfirmed partial responses pending confirmation. **Includes 1 patient who died prior to their first response assessment. †Includes only confirmed responses. ‡Unstable median, based on fewer than 10% of total number of events. Total % may be different than the sum of the individual components due to rounding. Abbreviations: NE, not estimable; PFS, progression-free survival.

Shah M, *et al*. J Clin Oncol 38:2020 (suppl; abstr 3594) Courtesy of Dr M Shah.

Selpercatinib safety profile

Adverse event	LIBRETTO-001 safety database, n=531							
	Treatment-emergent AEs (≥15% overall)					Treatment-related AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Dry mouth	29%	4%	–	–	32%	–	–	27%
Diarrhea	21%	8%	2%	–	31%	1%	–	16%
Hypertension	4%	11%	14%	<1%	29%	8%	<1%	18%
Increased AST	17%	5%	6%	1%	28%	4%	1%	22%
Increased ALT	13%	4%	7%	1%	26%	6%	1%	21%
Fatigue	15%	9%	1%	–	24%	<1%	–	14%
Constipation	19%	3%	<1%	–	22%	<1%	–	11%
Headache	15%	4%	1%	–	20%	<1%	–	7%
Nausea	15%	4%	<1%	–	19%	<1%	–	8%
Peripheral edema	16%	4%	<1%	–	19%	–	–	10%
Increased creatinine	14%	4%	–	<1%	18%	–	–	10%

- 9 patients (1.7%) discontinued due to treatment-related toxicity

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ORIGINAL ARTICLE

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

Lori J. Wirth, M.D., Eric Sherman, M.D., Bruce Robinson, M.D., Benjamin Solomon, M.B., B.S., Ph.D., Hyunseok Kang, M.D., Jochen Lorch, M.D., Francis Worden, M.D., Marcia Brose, M.D., Ph.D., Jyoti Patel, M.D., Sophie Leboulleux, M.D., Yann Godbert, M.D., Fabrice Barlesi, M.D., Ph.D., et al.

N Engl J Med 2020; 383:825-835

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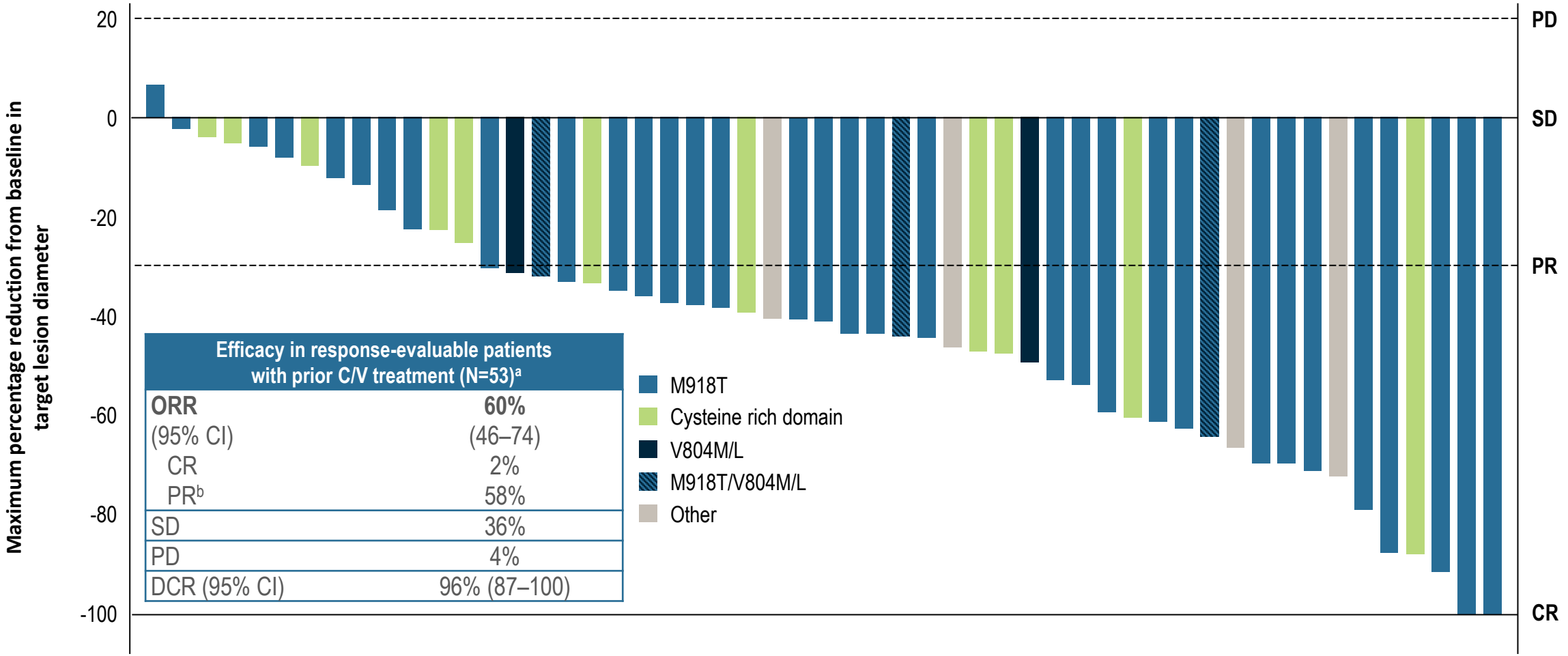
Results from the registrational phase 1/2 ARROW trial of pralsetinib (BLU-667) in patients with advanced *RET* mutation-positive medullary thyroid cancer

Mimi I. Hu[1], Vivek Subbiah[1], Lori Wirth[2], Martin Schuler[3], Aaron S. Mansfield[4], Marcia S. Brose[5], Giuseppe Curigliano[6], Sophie Leboulleux[7], Viola W. Zhu[8], Bhumsuk Keam[9], Ignacio Matos[10], Chia-Chi Lin[11], Douglas Adkins[12], Christina S. Baik[13], Gilberto Lopes[14], Yann Godbert[15], Debashis Sarker[16], Hui Zhang[17], Christopher D. Turner[17], Matthew H. Taylor[18]

[1]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [2]Massachusetts General Hospital, Boston, Massachusetts, USA; [3]West German Cancer Center, University Hospital Essen, Essen, Germany; [4]Mayo Clinic, Rochester, Minnesota, USA; [5]Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [6]European Institute of Oncology, IRCCS, and University of Milano, Milan, Italy; [7]Gustave Roussy, Villejuif, France; [8]University of California, Irvine School of Medicine, Orange, California, USA; [9]Seoul National University Hospital, Seoul, Republic of South Korea; [10]Vall d' Hebron Institute of Oncology, Barcelona. Spain; [11]National Taiwan University Hospital, Taipei, Taiwan; [12]Washington University School of Medicine, St. Louis, Missouri, USA; [13]University of Washington School of Medicine, Seattle, Washington, USA; [14]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, Florida, USA; [15]Bergonié Institute Cancer Center, Bordeaux, France; [16]Guy's Hospital, King's College London, London, UK; [17]Blueprint Medicines Corporation, Cambridge, Massachusetts, USA; [18]Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, Oregon, USA

Clinical response to pralsetinib in patients with prior cabozantinib and/or vandetanib treatment

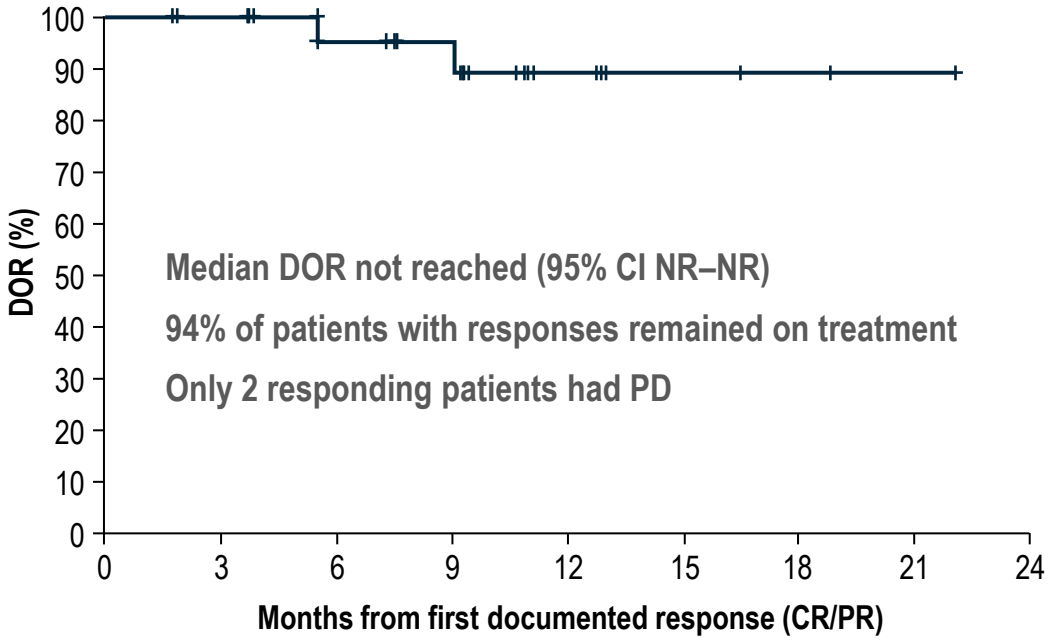


Efficacy in response-evaluable patients with prior C/V treatment (N=53)[a]	
ORR	**60%**
(95% CI)	(46–74)
CR	2%
PR[b]	58%
SD	36%
PD	4%
DCR (95% CI)	96% (87–100)

[a]Blinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. Six patients without measurable disease at baseline on central review, and 2 patients without a post-baseline tumor response assessment were not response evaluable. [b]1 PR pending confirmation. C/V, cabozantinib and/or vandetanib; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

▪DOR and PFS with pralsetinib in patients with prior cabozantinib and/or vandetanib treatment

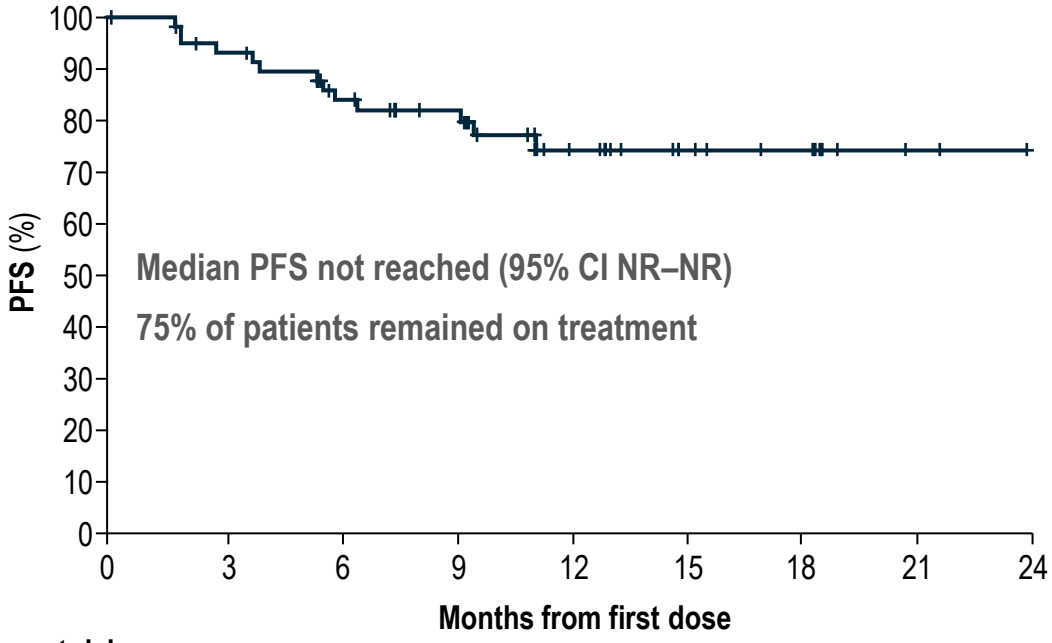
DOR



Numbers at risk

31	28	20	17	7	3	2	1	0

PFS



Numbers at risk

61	53	43	36	22	11	8	2	0

▪Blinded independent central review of tumor response; Patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. DOR presented for response-evaluable population and includes confirmed responses only; PFS presented for efficacy population.

▪DOR, duration of response; NR, not reached; PFS, progression-free survival.

NTRK INHIBITORS IN THYROID CANCER

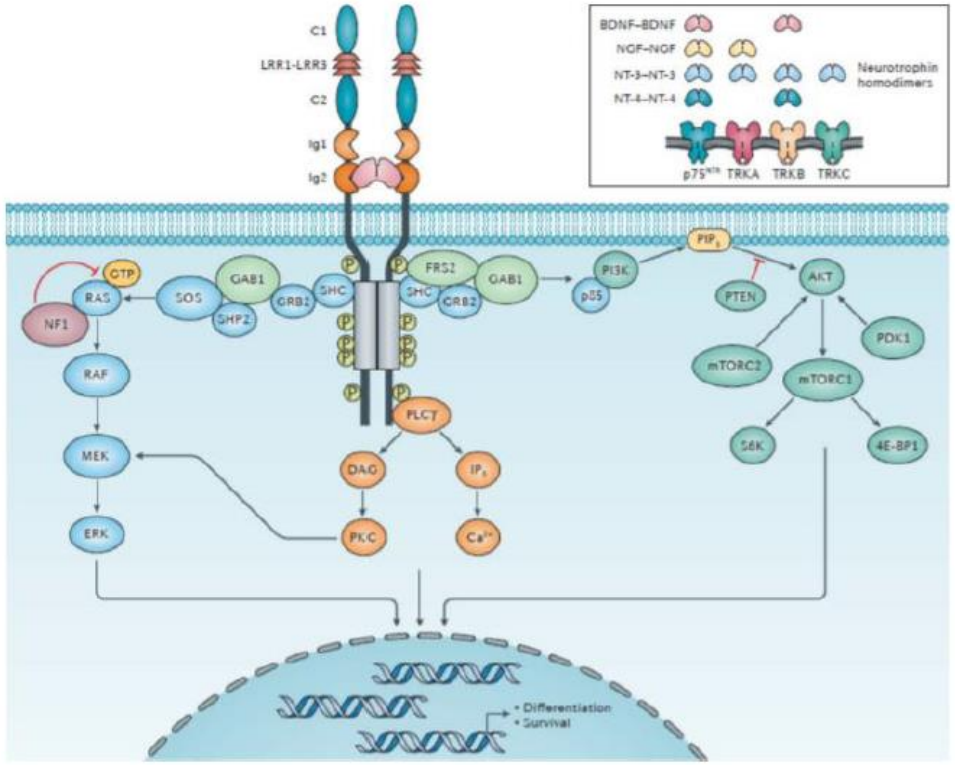
NTRK1-3 (Neurotrophic Tyrosine Receptor Kinase): Encoding for transmembrane Tropomyosin Receptor Kinase: TRKA, TRKB, TRKC.

Physiologic functions: Differentiation and survival of neurons, synapse formation and plasticity, membrane trafficking, formation of axons and dendrites

NTRK gene fusions are targetable genetic alterations that code for fusion proteins that lead constitutive activation of signalling pathways

Thyroid cancer has a frequency of TRK fusions between 5–25%

First-generation TRK inhibitors: Larotrectinib and entrectinib



Reprinted by permission from Springer Nature, Nat Rev Clin Oncol, *NTRK* fusion-positive cancers and TRK inhibitor therapy, Cocco E, *et al*. Copyright 2018; Kummar S. Target Oncol 2018;13:545–56; Drilon A, *et al*. N Engl J Med 2018;378:731–9; Drilon A, *et al*. Cancer Discovery 2017;7:400–9

NTRK INHIBITORS IN THYROID CANCER

ENTRECTINIB:[1] Analysis of three Phase 1/2 trials

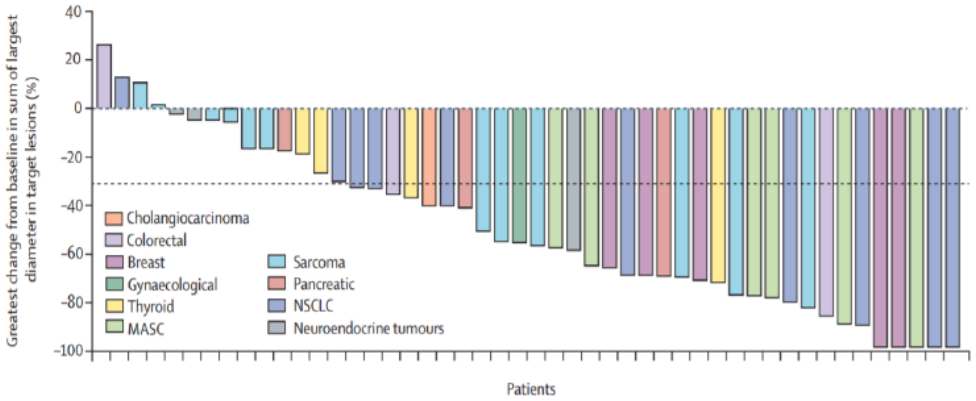
N=54 (Thyroid n=5)

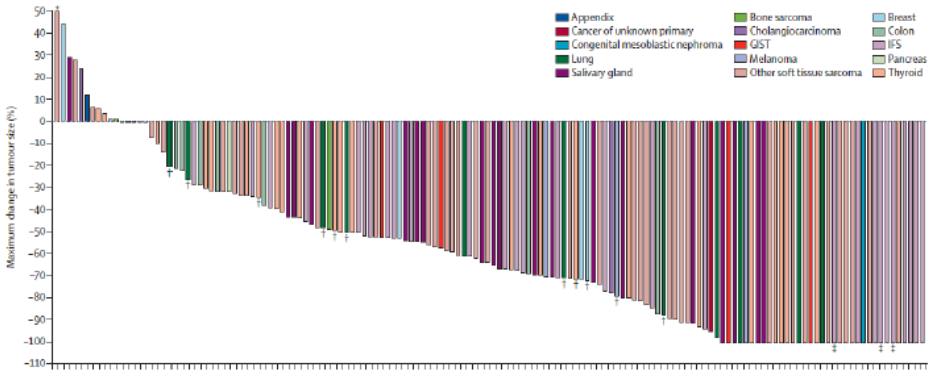
ORR = 57% (CR = 7%)
PD = 7%
mPFS = 11.2 months (8.0, 14.9)

LAROTRECTINIB:[2] Analysis of three Phase 1/2 trials

N=153 (Thyroid n=24)

ORR = 79% (CR = 16%) → Thyroid (ORR = 79%)
PD = 6%
mPFS = 18.3 months (22.1, NE)





1. Reprinted from Lancet Oncology, 21(2), Doebele RC, *et al.* Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials, 271–82. Copyright 2020, with permission from Elsevier; 2. Reprinted from Lancet Oncol, 21(4), Hong DS, *et al.* Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials, 531–40. Copyright 2020 with permission from Elsevier.

- Confirmation de l'importance des **thérapies ciblées anti-RET** avec changement de pratique à prévoir dans la prise en charge de première ligne du CMT métastatique progressif de fort volume tumoral (étude de phase 3 en cours)

- Impact potentiel important d'un **screening moléculaire large** en cas d'échappement aux anti-VEGF dans les cancers thyroïdiens de souche folliculaire, avec notamment recherche des fusions de RET, ALK, NTRK et mutation de BRAF