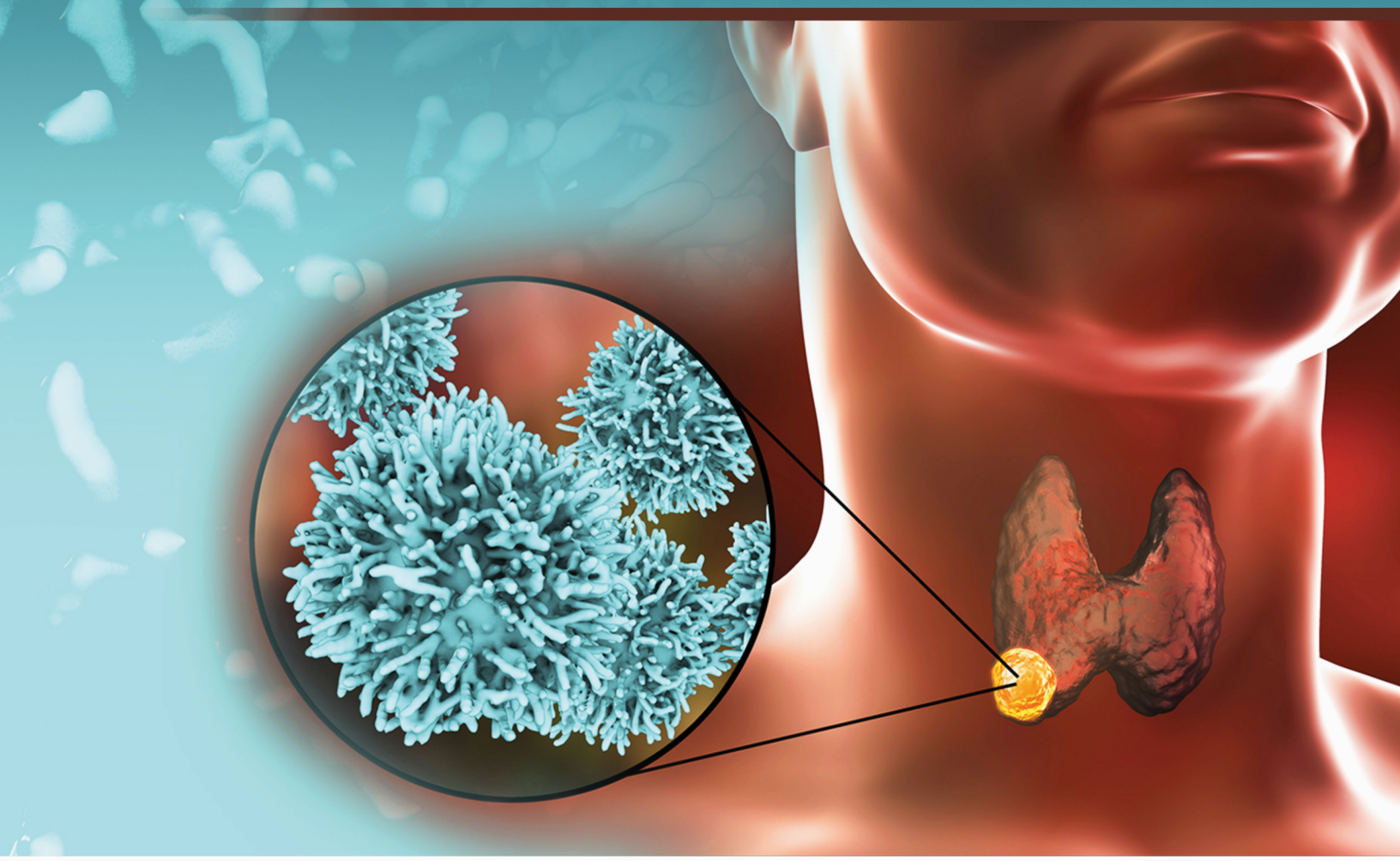
Precision Medicine in Action:

Using Thyroid Cancer Biomarkers to Match the Right Patient with the Right Treatment at the Right Time



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Precision Medicine in Action: Using Thyroid Cancer Biomarkers to Match the Right Patient with the Right Treatment at the Right Time

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PROGRAM OVERVIEW

This live virtual activity will cover the diagnosis, treatment, and management of advanced thyroid cancer.

TARGET AUDIENCE

This educational activity is intended for oncologists and endocrinologists, as well as pathologists, along with their multidisciplinary teams in academic centers and the community setting who are especially challenged in keeping up with the most current data on new and emerging, less commonly occurring genomic alterations, genomic testing methodologies, and optimal treatment decisions for patients with thyroid cancer.

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Utilize best practices for identifying actionable thyroid cancer molecular/genomic alterations in routine clinical practice.
- Integrate available and emerging targeted treatment options into routine clinical practice for the treatment of patients with advanced thyroid cancer based on results showing actionable molecular/genomic alterations.

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in caring for patients with advanced thyroid cancer.

Credit: 1.0 ANCC Contact Hour

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Mark Zafereo, MD, FACS	Research Funding	Eli Lilly and Merck
Shereen Ezzat, MD, FRCP(C), FACP	No relevant relationships with a manufacturer or commercial entity.	
Jaume Capdevila, MD, PhD	Speakers Bureau	Ipsen, Pfizer, Novartis, Lilly, Exelixis, Merck Serono, Adacap, Eisai, Bayer, Sanofi
	Consultant	Ipsen, Pfizer, Novartis, Lilly, Exelixis, Merck Serono, Adacap, Eisai, Bayer, Sanofi

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The reviewer of this activity has nothing to disclose.

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1. Read the CME/CNE information and faculty disclosures
2. Participate in the live virtual activity
3. Submit the pre- and post-test and evaluation form to Med Learning Group

You will receive your certificate as a downloadable file.

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Agenda

Precision Medicine in Action: Using Thyroid Cancer Biomarkers to Match the Right Patient with the Right Treatment at the Right Time

I. **Epidemiology**

II. **Histological subtypes**
   a. Pathophysiology and disease course
   b. Traditional standard of care therapies for advanced thyroid cancer
   c. Advantages and disadvantages associated with the traditional watch-and-wait approach

III. **Molecular/Genomic Alterations Associated with Thyroid Cancer**
   a. *RET* mutations as an example **(Whiteboard Theme: MOA of *RET* mutations in the development of thyroid cancer)**
   b. Types of tests available to detect actionable molecular/genomic alterations in patients with thyroid cancer
   c. Guidance on which tests should be used, when they should be used, and which patients should be tested
   d. Best practices pertaining to processes and workflows for integrating routine molecular/genomic testing into clinical practice

IV. **Applying Precision Medicine Approaches to Treating Patients with Advanced Thyroid Cancer**
   a. Available targeted therapeutic options for patients with advanced thyroid cancer **(Whiteboard Theme: MOA of selpercatinib in the treatment of patients with advanced or metastatic *RET*-mutant MTC or *RET* fusion-positive thyroid cancer)**
   b. Efficacy and safety profiles of available and emerging targeted therapeutic options for patients with advanced thyroid cancer
   c. Integrating available and emerging targeted therapeutic options for patients with advanced thyroid cancer into clinical practice

V. **Conclusion**
   a. Moving forward
   b. Q&A

Precision Medicine in Action: Using Biomarkers to Match The Right Patient with the Right Treatment at the Right Time: Grand Round Series

Disclosures

- During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

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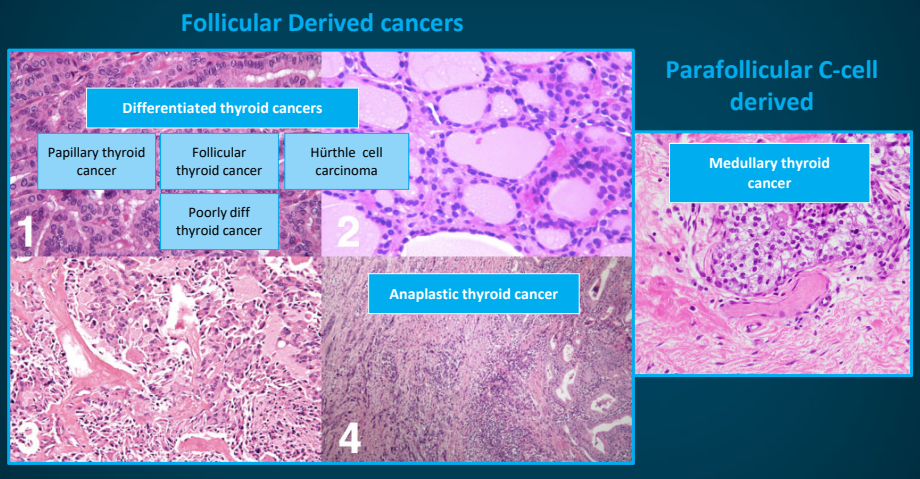
Educational Objectives

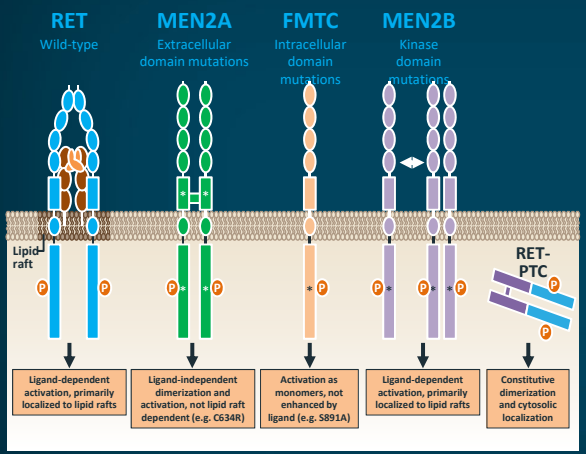
- Utilize best practices for identifying actionable thyroid cancer molecular/genomic alterations in routine
- Integrate available and emerging targeted treatment options into routine clinical practice of patients with advanced thyroid cancer based on results showing actionable molecular/genomic alterations

The Array of Thyroid Cancers



White Board Animation – Mechanism of RET mutations in thyroid cancer

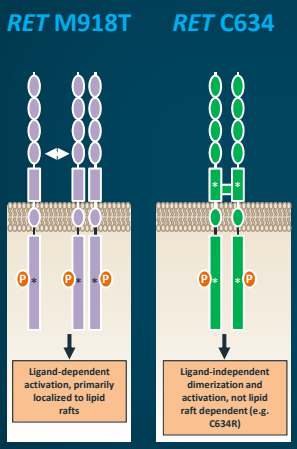
RET Proto-Oncogene



- *RET* proto-oncogene encodes transmembrane receptor tyrosine kinase
- Activated in thyroid cancer via 2 distinct mechanisms:
- *RET* mutations in cysteine-rich extracellular or kinase domains
- Gene rearrangement → fusion of *RET* to 5' upstream partner
- Both → ligand-independent signaling & oncogenesis

Mulligan, *Nature Rev Cancer*, 2014; Subbiah, et al. *J Clin Oncol*, 2020

Most Common *RET* Alterations in Medullary Thyroid Cancer (MTC)

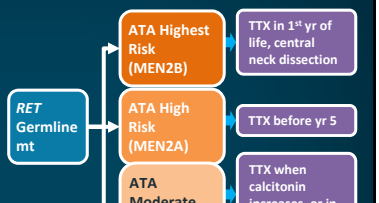


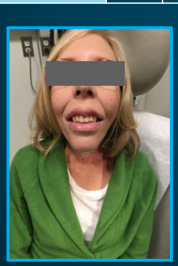
- *RET* mutations drive 70% of MTCs
- 25% of MTC are hereditary – all patients have germline *RET* mutations
- 60% of sporadic MTCs harbor somatic *RET* mutations
- *RET* M918T most common somatic mutation
- Germline *RET* M918T occurs in nearly all MEN 2B patients
- Germline *RET* C634 most common hereditary mutation (MEN 2A)
- *RET* C634 can also occur somatically

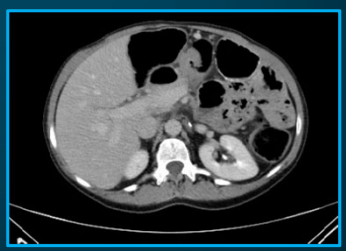
Ciampi, et al. *iScience*, 2019; Mulligan, *Nature Rev Cancer*, 2014

Genotype-Phenotype Correlation in Hereditary *RET*

RET mutation	Exon	MTC risk level	Incidence of PHEO	Incidence of HPTH	CLA	HD
G533C	8	MOD	+	–	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C61 1F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618E/R/S	10	MOD	+/++	+	N	Y
C620F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	Y	N
V804M	14	MOD	+	+	N	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N



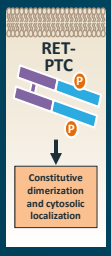


Phay, *Semin Surg Oncol*, 2000; Wells, *Thyroid*, 2015

RET Fusion-Driven Thyroid Cancer

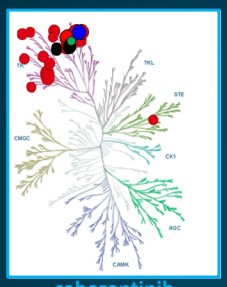
CCDC6-RET



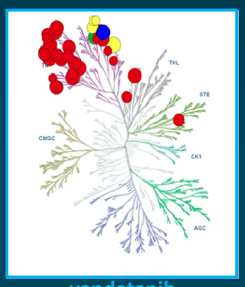
- *RET* fusions in < 10% of PTCs
- More frequent in pediatric and young adult cancers, ~30%
- 58% in pediatric Chernobyl-induced cancers
- *CCDC6-RET* (*RET/PTC1*) & *NCOA4-RET* (*RET/PTC3*) are most common fusions
- More than twenty 5' fusion partners have now been described

TCGA, *Cell*, 2014; Vanden Borre, *Oncologist*, 2017; Ricarte-Filho, *J Clin Invest*, 2013

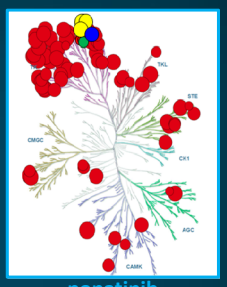
Kinome Selectivity For MKIs With RET Activity



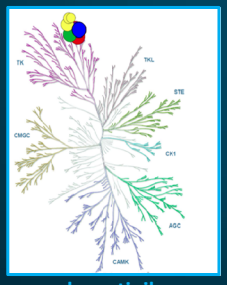
cabozantinib



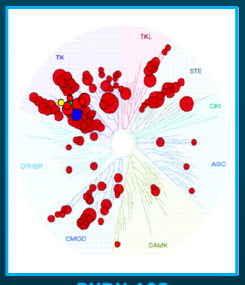
vandetanib



ponatinib



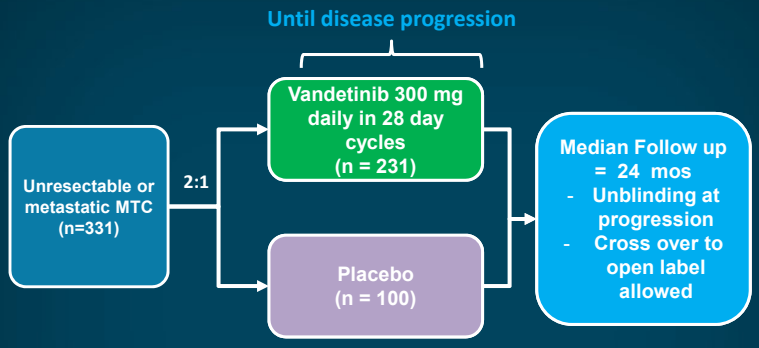
lenvatinib



RXDX-105

RET
KDR/VEGFR2
FGFR1-3/EGFR
MET/ALK/ROS
Other kinases

Vandetinib in Metastatic Medullary Thyroid Cancer



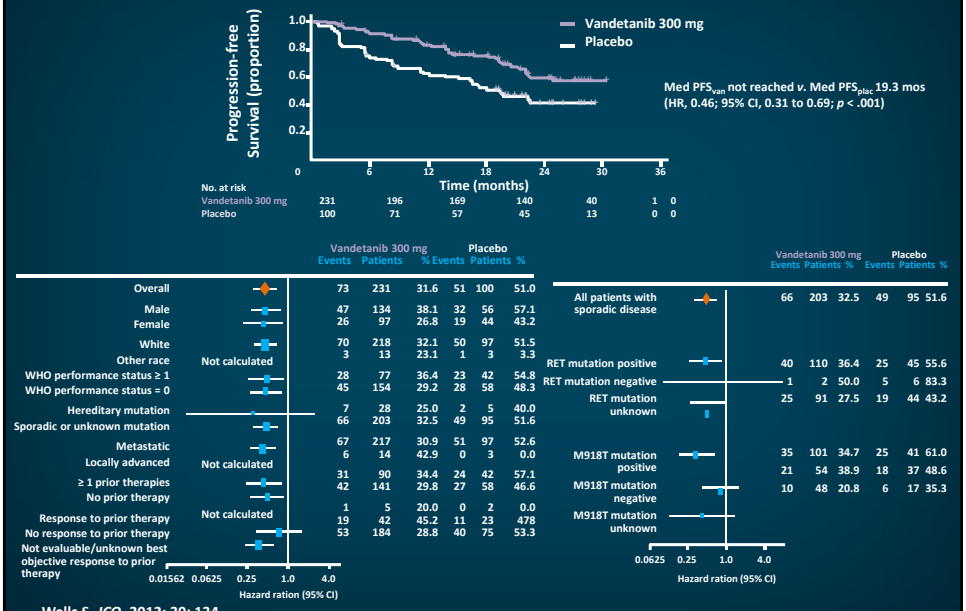
Key eligibility criteria

- RECIST-measurable disease
- PS 0-2
- Serum calcitonin ≥ 500 pg/mL
- No more than one prior therapy with a TKI

- Primary endpoint – progression free survival (PFS)
- Secondary endpoints – overall survival (OS), overall response rate (ORR), and safety
- Of 298 pts with sporadic MTC
  - 52.0% RET mutation positive
  - 45.3% RET unknown
  - 2.7% No RET mutation

Wells S. JCO. 2012; 30: 134.

Vandetanib Results in MTC



Wells S. *JCO*. 2012; 30: 134.

Vandetanib – Safety and Tolerability in MTC

Common Adverse Events (safety

Adverse Event	Vandetanib (n=231)		Placebo (n=99)	
	No.	%	No.	%
Any grade occurring with an incidence = 10% overall				
Diarrhea	130	56	26	26
Rash	104	45	11	11
Nausea	77	33	16	16
Hypertension	73	32	5	5
Fatigue	55	24	23	23
Headache	59	26	9	9
Decreased appetite	49	21	12	12
Acne	46	20	5	5
Asthenia	34	14	11	11
Vomiting	34	14	7	7
Back pain	21	9	20	20
Dry skin	35	15	5	5
Insomnia	30	13	10	10
Abdominal pain	33	14	5	5
Dermatitis acneiform	35	15	2	2
Cough	25	10	10	10
Nasopharyngitis	26	11	9	9
ECG QT prolonged*	33	14	1	1
Weight decreased	24	10	9	9

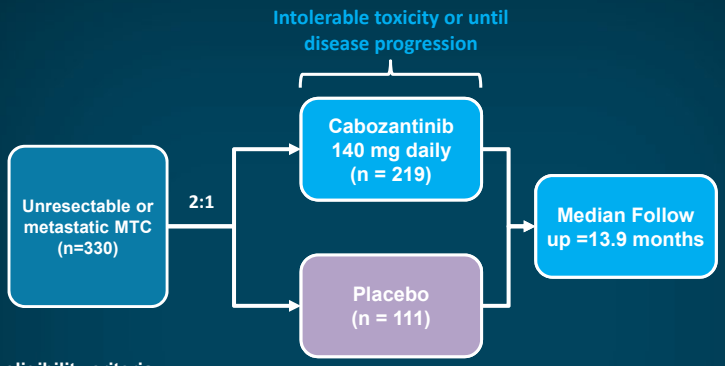
Adverse Event	Vandetanib (n=231)		Placebo (n=99)	
	No.	%	No.	%
Grade 3+ occurring with an incidence of ≥ 2% on either arm				
Diarrhea	25	11	2	2
Hypertension	20	9	0	–
ECG QT prolonged*	18	8	1	1
Fatigue	13	6	1	1
Decreased appetite	9	4	0	–
Rash	8	4	1	1
Asthenia	6	3	1	1
Dyspnea	3	1	3	3
Back pain	1	0.4	3	3
Syncope	0	–	2	2

Prolonged QTc – vandetanib is only available through REMS program.

*As defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v3 (see Results for the incidence of protocol-defined QTc prolongation as described in Methods, Safety and Tolerability).

Wells S. *JCO*. 2012; 30: 134.

Cabozantinib in Progressive, Metastatic MTC



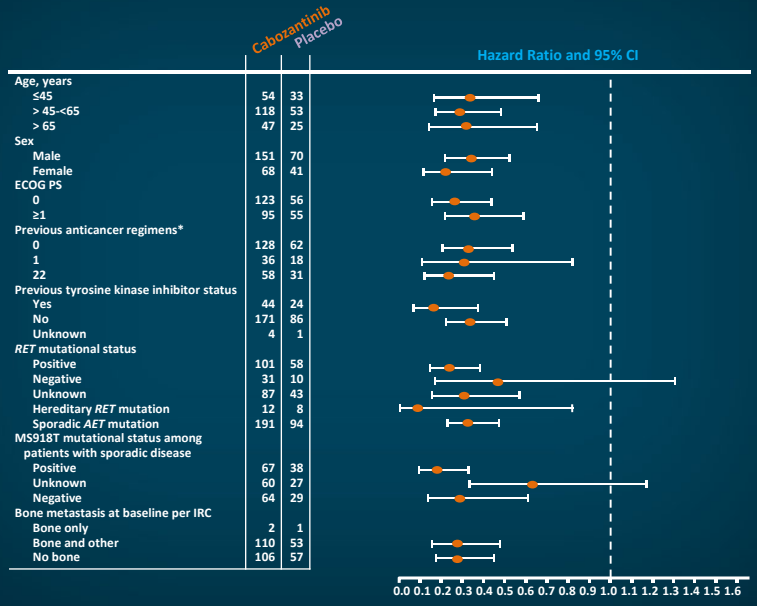
Key eligibility criteria

- Definitively diagnosed non-resectable
- RECIST-measurable progressive disease
- No restriction on prior therapy, including other TKIs

- Primary endpoint – progression free survival (PFS)
- Secondary endpoints – tumor response rate, overall survival (OS), overall response rate (ORR), and safety
- RET mutation positive = 49.2% and negative = 12%
- RET status unknown = 39%

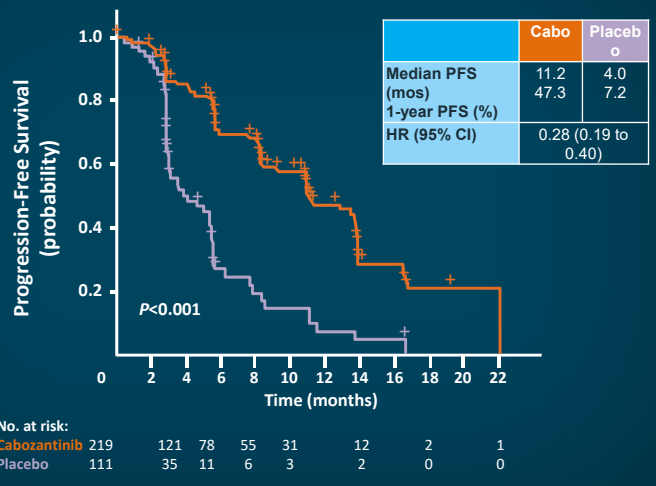
Elisei R. *JCO*. 2013; 31: 3639.

Progression Free Survival Analysis



Elisei R. *JCO*. 2013; 31: 3639.

Progression Free Survival Analysis
(continued)



	Cabo	Placebo
Median PFS (mos)	11.2	4.0
1-year PFS (%)	47.3	7.2
HR (95% CI)	0.28 (0.19 to 0.40)	

Elisei R. *JCO*. 2013; 31: 3639.

Safety Analysis and Adverse Events

AEs Occurring in ≥ 10% of Cabozantinib-Treated Patients, by Maximum Severity Reported

	Cabozantinib (n=214)				Placebo (n=109)			
	All Grades		Grade ≥3		All Grades		Grade ≥3	
Adverse Events	No.	%	No.	%	No.	%	No.	%
Diarrhea	135	63.1	34	15.9	36	33.0	2	1.8
Palmar-plantar erythrodysesthesia*	107	50.0	27	12.6	2	1.8	0	—
Decreased weight	102	47.7	10	4.7	11	10.1	0	—
Decreased appetite	98	45.8	10	4.7	17	15.6	1	0.9
Nausea	92	43.0	3	1.4	23	21.1	0	—
Fatigue	87	40.7	20	9.3	31	28.4	3	2.8
Dysgeusia	73	34.1	1	0.5	6	5.5	0	—
Hair color changes	72	33.6	1	0.5	1	0.9	0	—
Hypertension	70	32.7	18	8.4	5	4.6	1	0.9
Stomatitis	62	29.0	4	1.9	3	2.8	0	—
Constipation	57	26.6	0	—	6	5.5	0	—
Hemorrhage	54	25.2	7	3.3	17	15.6	1	0.9
Vomiting	62	24.3	5	2.3	2	1.8	1	0.9
Mucosal inflammation	50	23.4	7	3.3	4	3.7	0	—
Asthenia	45	21.0	12	5.6	16	14.7	2	1.8
Dysphonia	43	20.1	0	—	10	9.2	0	—
Rash	41	19.2	2	0.9	11	10.1	0	—
Dry skin	41	19.2	0	—	3	2.8	0	—
Headache	39	18.2	1	0.5	9	8.3	0	—
Oropharyngeal pain	38	17.8	1	0.5	5	4.6	0	—
Abdominal pain	36	16.8	6	2.8	7	6.4	1	0.9
Alopecia	35	16.4	0	—	2	1.8	0	—
Pain in extremity	33	15.4	3	1.4	12	11.0	1	0.9
Back pain	32	15.0	5	2.3	12	11.0	1	0.9
Dyspnea	29	13.6	5	2.3	19	17.4	11	10.1
Arthralgia	29	13.6	2	0.9	8	7.3	0	—

AEs Associated With VEGF Pathway Inhibition

	Cabozantinib (n=214)				Placebo (n=109)			
	All Grades		Grade ≥3		All Grades		Grade ≥3	
Adverse Events	No.	%	No.	%	No.	%	No.	%
Hypertension	70	32.7	18	8.4	5	4.6	1	0.9
Hemorrhage	54	25.2	7	3.3	17	16.6	1	0.9
Venous thrombosis	12	5.6	8	3.7	3	2.8	2	1.8
GI perforation	7	3.3	7	3.3	0	—	0	—
GI fistula	2	0.9	1	0.5	0	—	0	—
Abdominal/pelvic abscess	5	2.3	2	0.9	0	—	0	—
Non-GI fistula	8	3.7	4	1.9	0	—	0	—
Arterial thrombosis	5	2.3	2	0.9	0	—	0	—
Proteinuria	4	1.9	2	0.9	0	—	0	—
Wound complication	4	1.9	2	0.9	1	0.9	0	—
Osteonecrosis	3	1.4	1	0.5	0	—	0	—
RPLS	1	0.5	1	0.5	0	—	0	—

Treatment-related AEs:
- 79% of cabo pts had dose reductions
- 16% of cabo pts had dose discontinued

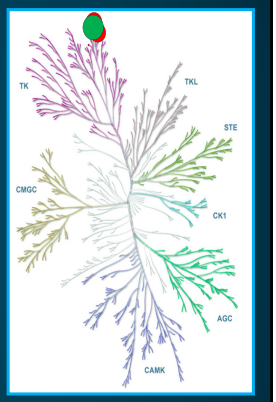
Elisei R. *JCO*. 2013; 31: 3639.

RPLS, reversible posterior leukoencephalopathy syndrome; VEGF, vascular endothelial growth factor.

Honing in on RET

- 2 new highly potent and specific RET inhibitors now completed first-in-human trials
  - Selpercatinib (LOXO-292)
  - Pralsetinib (BLU-667)
- Both designed to potently inhibit
  - wt RET fusions (in PTC, NSCLC, etc)
  - Oncogenic RET mutations (in MTC)
  - And V804 acquired gatekeeper mt, to prevent emergence of acquired resistance
- With little activity against KDR/VEGFR-2
- Efficacy of other MKIs may be limited by insufficient RET inhibition as toxicity from dose limiting off target effects, esp. at KDR, limiting RET blockade

LOXO-292



White Board Animation – MOA of selpercatinib in advanced/metastatic disease

LIBRETTO-001

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

- LIBRETTO-001: open-label phase 1-2 trial, 65 centers, 12 countries
- 3 thyroid cohorts:
  - *RET*-mt MTC, previously treated with vandetinib +/or cabozantinib
  - *RET*-mt MTC, not previously treated with vandetinib +/or cabozantinib
  - *RET* fusion-positive previously treated thyroid cancer

Wirth L. *N Engl J Med*. 2020;383: 825-835.

Patient Characteristics

- RET-mt MTC, previously treated: n = 55
  - 60% RET M918T
  - 13% extracellular cysteine-rich domain mt
  - Familial and sporadic patients enrolled
- *RET*-mt MTC, not previously treated: n = 88
- RET fusion+ thyroid cancer: n = 19
  - PTC, PDTC, ATC, HCC
  - 47% CCDC6-RET
  - 32% NCOA4-RET

Wirth L. *N Engl J Med*. 2020;383: 825-835.

Patient Characteristics

Characteristics	*RET*-Mutant MTC Previously Treated (N=55)	*RET*-Mutant MTC Not Previously Treated (N=88)	Previously Treated *RET* Fusion—Positive Thyroid Cancer (N-19)
Median age (range) — yr	57 (17-84)	58 (15-82)	54 (25-88)
Sex— no. (%)			
Male	36 (65)	58 (66)	9 (47)
Female	19 (35)	30 (34)	10 (53)
Race — no. (%)†			
White	49 (89)	75 (85)	14 (74)
Asian	0	4 (5)	2 (11)
Black	1 (2)	1 (1)	1 (5)
Other	5 (9)	8 (9)	2 (11)‡
ECOG performance-status score — no. (%)			
0	11 (20)	43 (49)	5 (26)
1	41 (75)	42 (48)	12 (63)
2	3 (5)	3 (3)	2 (11)
Histologic type of thyroid cancer			
Medullary	55 (100)	88 (100)	—
Papillary	—	—	13 (68)
Poorly differentiated	—	—	3 (16)
Hürthle cell	—	—	1 (5)
Anaplastic	—	—	2 (11)
Median no. of previous systemic regimens (range)	2 (1-8)	0 (0-2)	4 (1-7)
Previous regimen — no. (%)			
Cabozantinib, vandetanib, or both	55 (100)	0	—
Vandetanib only	18 (33)	0	—
Cabozantinib only	13 (24)	0	—
Cabozantinib and vandetanib	24 (44)	0	—
Radioiodine	—	—	16 (84)
Sorafenib, lenvatinib, or both	—	—	13 (68)
Muktitargeted kinase inhibitor therapy	55 (100)	7 (8)	15 (79)
1	26 (47)	6 (7)	7 (37)
≥2	29 (53)	1 (1)	8 (42)
Therapy other than multitargeted kinase inhibitor therapy	17 (31)	9 (10)	14 (74)
Brain metastases — no. (%)	4 (7)	2 (2)	6 (32)
RET alteration — no. (%)			
RET M918T mutation	33 (60)	49 (36)	—
RET V804 M/L mutation	5 (9)	6(7)	—
RET extracellular cysteine mutation	7 (13)	20 (23)	—
Other mutations	10 (18)	13 (15)	—
CCDC6-RET fusion	—	—	9 (47)
NCOA4-RET fusion	—	—	6 (32)
Other *RET* fusion	—	—	4 (21)

Wirth L. *N Engl J Med*. 2020;383: 825-835.

Selpercatinib Safety Profile in Thyroid Patients

- Most common ≥ gr 3/4 treatment-related AEs
  - HTN
  - Transaminitis
  - Diarrhea
- 30% patients had dose reduction d/t TRAE
- 2% discontinued selpercatinib d/t TRAE

Selpercatinib Safety Profile in Thyroid Patients
(continued)

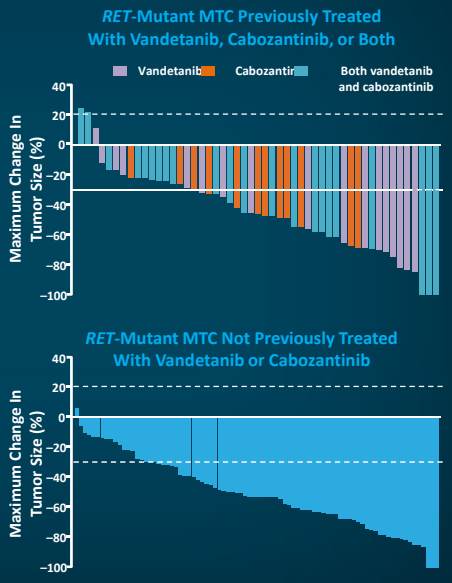
AEs reported in ≥ 15%

Adverse Events	Adverse Events, Regardless of Attribution					Treatment-Related Adverse Events		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	Number of patients (percent)							
Any adverse event	9 (6)	42 (26)	95 (59)	11 (7)	162 (100)	45 (28)	3 (2)	153 (94)
Dry mouth	69 (43)	5 (3)	0	0	74 (46)	0	0	63 (39)
Hypertension	10 (6)	25 (15)	34 (21)	0	69 (43)	19 (12)	0	49 (30)
Diarrhea	44 (27)	8 (5)	9 (6)	0	61 (38)	4 (3)	0	27 (17)
Fatigue	35 (22)	24 (15)	2 (1)	0	61 (38)	1 (1)	0	41 (25)
Increased aspartate aminotransferase level	37 (23)	6 (4)	13 (8)	1 (1)	57 (35)	12 (7)	1 (1)	45 (28)
Nausea	44 (27)	13 (8)	0	0	57 (35)	0	0	25 (15)
Constipation	44 (27)	11 (7)	1 (1)	0	56 (35)	0	0	26 (16)
Increased alanine aminotransferase level	26 (16)	7 (4)	17 (10)	1 (1)	51 (31)	16 (10)	1 (1)	42 (26)
Headache	36 (22)	11 (7)	4 (2)	0	51 (31)	1 (1)	0	21 (13)
Peripheral edema	42 (26)	5 (3)	1(1)	0	48 (30)	0	0	29 (18)
Increased blood creatinine level	27 (17)	12 (7)	0	0	39 (24)	0	0	22 (14)
Abdominal pain	25 (15)	8 (5)	5 (3)	0	38 (23)	0	0	6 (4)
Arthralgia	25 (15)	10 (6)	0	0	35 (22)	0	0	8 (5)
Vomiting	26 (16)	8 (5)	1(1)	0	35 (22)	0	0	12 (7)
Hypocalcemia	14 (9)	13 (8)	6 (4)	1 (1)	34 (21)	0	0	5 (3)
Back pain	19 (12)	10 (6)	2 (1)	0	31 (19)	0	0	1 (1)
QT interval prolonged on electrocardiography	11 (7)	16 (10)	4 (2)	0	31 (19)	3 (2)	0	21 (13)
Cough	25 (15)	4 (2)	0	0	29 (18)	0	0	2 (1)
Rash	25 (15)	3 (2)	0	0	28 (17)	0	0	13 (8)
Dizziness	25 (15)	2 (1)	0	0	27 (17)	0	0	9 (6)
Abdominal distension	18 (11)	7 (4)	0	0	25 (15)	0	0	12 (7)
Hypothyroidism	14 (9)	11 (7)	0	0	25 (15)	0	0	12 (7)
Weight increased	11 (7)	9 (6)	5 (3)	0	25 (15)	1 (1)	0	8 (5)

Selpercatinib Efficacy in MTC

Objective response rate per RECIST v1.1, determined by independent review committee

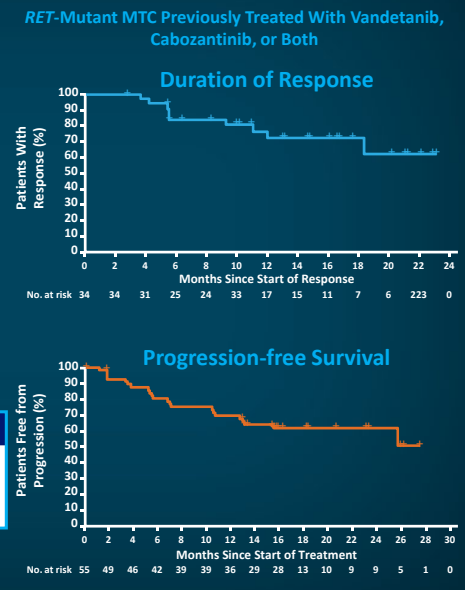
- *RET*-mt MTC, previously treated:
  - ORR = 69% (95% CI, 55 to 81)
  - CR = 9%, PR = 60%
- *RET*-mt MTC, not previously treated:
  - ORR = 73% (95% CI, 62 to 82)
  - CR = 11%, PR = 61%
- Responses seen across all *RET* mts
  - incl *RET* V804



Selpercatinib Efficacy in MTC

Duration of response & progression-free survival

- Median DOR not yet reached
  - (95% CI, 19.1 mos to NE)
  - Median follow-up = 14.1 mos
- Median PFS not yet reached
  - Median follow-up = 16.7 mos
  - (95% CI, 24.4 mos to NE)

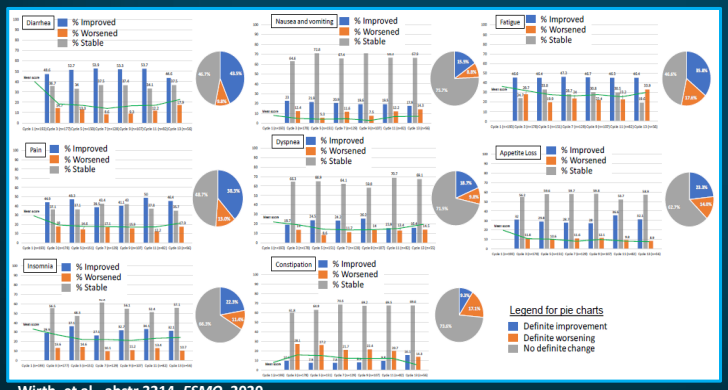


LIBRETTO-001 Patient-Reported Outcomes in MTC

- EORTC QLQ-C30 & Modified Systemic-therapy Induced Diarrhea Assessment Tool (mSTIDAT)

Symptom subscales (QLQ-C30)[a]

Mean scores and proportion of patients meeting a clinically meaningful difference (CMD) by cycle of therapy (bar and line graphs)[b]
Proportion of patients meeting 'definite' improvement or worsening (pie charts)[c]

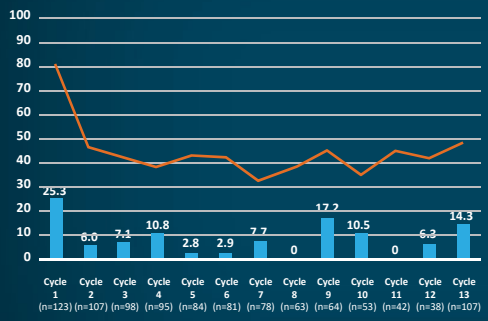


Wirth, et al., abstr 3214, *ESMO*, 2020

[a] Scored 0-100: lower Scores represent fewer symptoms
[b] Improved/Worsened: Each patent was categorized as 'improved' or "worsened" at each study visit if the CMD (decrease or increase of 210 paints, respectively) was met versus them baseline score, all other patients were "stable" if the CMD was not met
[c] Definite improvement/definite worsening: Each patent was categorized as having a "definite improvement' or "definite worsening' if the CMD (decrease or increase of 210 paints, respectively) was met versus this baseline score, and no further changes of 10 paints or more were observed at any subsequent assessment All remaining patents did not meet the criteria for 'definite' change in this study.

LIBRETTO-001 Patient-Reported Outcomes in MTC (continued)

Proportion of patients with diarrhea and severity, by cycle of therapy (mSTIDAT)



Line graph: proportion of patients experiencing diarrhea

Bar graph: proportion of those patients with diarrhea who indicate it as 'severe'

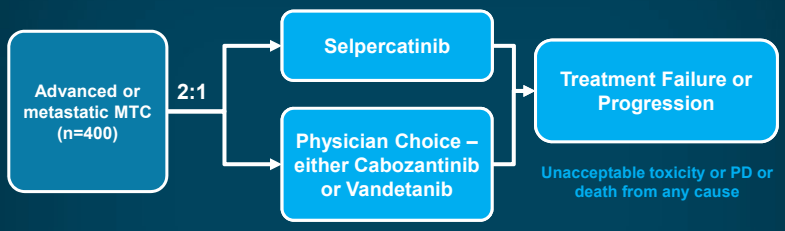
Conclusions:

- GI symptoms, esp. diarrhea, present at baseline
- After initiation of selpercatinib, pre-defined clinically meaningful ↓ in diarrhea by Cycle 3 seen
- Most patients improved or remained stable on each subscale of QLQ-C30
- Data suggest favorable tolerability of selpercatinib in *RET*-mutant MTC

Wirth, et al., abstr 3214, *ESMO*, 2020

Future Directions with Selpercatinib in MTC

LIBRETTO-531: A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice (Cabozantinib or Vandetanib) in Patients With Progressive, Advanced, Kinase Inhibitor Naïve, *RET*-Mutant MTC



Key eligibility criteria

- No prior systemic therapy for metastatic disease
- Age ≥ 12 years

- Primary endpoint – progression free survival (PFS)
- Secondary endpoints – treatment failure-free survival, overall survival (OS), duration of response rate (DOR), and safety
- Crossover to selpercatinib allowed at progression

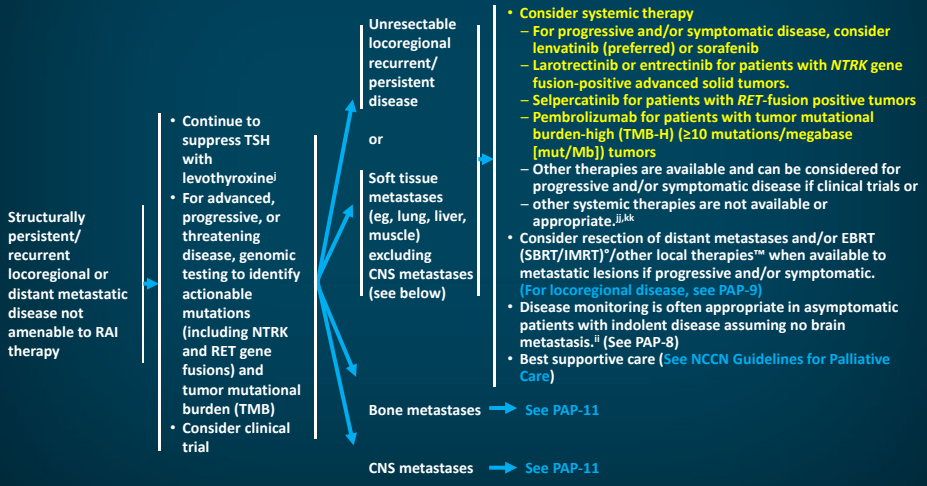
Clinicaltrials.gov. (LIBRETTO-531) NCT04211337.

MEDICAL SOCIETY GUIDANCE AND RECOMMENDATIONS

NCCN Guidelines Version 2.020

Thyroid Carcinoma – Papillary, Follicular, Hürthle Carcinoma

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY



NCCN Guidelines Version 2.2020

Thyroid Carcinoma – Medullary Carcinoma

RECURRENT OR PERSISTENT DISEASE DISTANT METASTASES

Asymptomatic disease

- Disease monitoring
- Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy)
- Systemic therapy if not resectable and progressing by RECIST criteria
  - Preferred Regimens
    - Vandetanib (category 1)
    - Cabozantinib (category 1)
    - Selpercatinib (*RET* mutation-positive)
  - Useful in Certain Circumstances
    - Pembrolizumab (TMB-H [210 mut/Mb])

Asymptomatic disease or progression

- Systemic therapy or clinical trial
  - Preferred Regimens
    - Vandetanib (category 1)
    - Cabozantinib (category 1)
    - Selpercatinib (*RET* mutation-positive)
  - Other Recommended Regimens
    - Consider other small-molecule kinase inhibitors
    - Dacarbazine (DTIC)-based chemotherapy
  - Useful in Certain Circumstances
    - Pembrolizumab (TMB-H [210 mut/Mb])
- EBRTI/IMRT for local symptoms
- Consider intravenous bisphosphonate or denosumab therapy for bone metastases
- Consider palliative resection, ablation (eg, RFA, embolization, other regional therapy), or other regional treatment
- Best supportive care

NCCN Guidelines Version 2.2020

Thyroid Carcinoma – Anaplastic Carcinoma

Systemic Therapy Regimens for Metastatic Disease

Preferred Regimens		
Dabrafenib/trametinib (*BRAF* V600E mutation positive)	Dabrafenib 150 mg PO ***AND*** Trametinib 2 mg PO	Twice daily Once daily
Larotrectinib (*NTRK* gene fusion positive)	100 mg PO	Twice daily
Entrectinib (*NTRK* gene fusion positive)	600 mg PO	Once daily
Selpercatinib (*RET* fusion positive)	120 mg PO (< 50 kg) ***OR*** 160 mg PO (2 50 kg)	Twice daily
Other Recommended Regimens		
Paclitaxel/carboplatin	Paclitaxel 60-100 mg/m^{2}carboplatinAUC2IV ***OR*** Paclitaxel 135-175 mg/m^2, carboplatin AUC 5-6 IV	Weekly Every 3-4 weeks
Docetaxel/doxorubicin	Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (with pegfilgrastim) ***OR*** Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV	Every 3-4 weeks Weekly
Paclitaxel	60-90 mg/m^2 ***OR*** 135-200 mg/m^2 IV	Weekly Every 3-4 weeks
Doxorubicin	60-75 mg/m^2 ***OR*** 20 mg/m^2 IV	Every 3 weeks Weekly
Useful in Certain Circumstances		
Lenvatinib (if not tolerating or no response to recommended agents in patients without curative option)	24 mg PO	Daily
Pembrolizumab (TMB-H [≥10 mut/Mb])	200 mg IV ***OR*** 400 mg IV	Every 3 weeks Every 6 weeks

ESMO - Clinical Practice Guidelines

Summary of recommendations (continued)

DTC (continued)

Systemic therapy and personalized medicine

- TSH suppression (serum level <0.1 μIU/mL) is recommended for all TC patients with persistent structural disease in the absence of specific contraindications [III, B]
- Decisions on whether of not to use MKIs must always be based on patient preference after a careful discussion with the managing physician of the
- expected benefits and risks associated with specific drugs
- Lenvatinib and sorafenib should be considered the standard first-line systemic therapy for RAI-refractory DTC [I, A; ESMO-MCBS v1.1 scores: 3 for lenvatinib, 2 for sorafenib)

ATC

Systemic therapy and personalized medicine

- Clinical trial enrolment should be encouraged for patients with good clinical PS [V, B]
- Patients with BRAF V600E-positive malignancies should be treated with the BRAF inhibitor dabrafenib (150 mg twice daily) plus the MEK inhibitor trametinib (2 mg once daily) if they are available [V, B]

MTC

Systemic therapy and personalized medicine

- Cabozantinib [I, A] and vandetanib [I, A; ESMO-MCBS v1.1 score: 2] are the first-line systemic therapy for patients with progressive, metastatic MTC
- In patients with RETM9I8T of RAS-mutant MTCs, cabozantinib offers significant PFS and OS advantages over wild-type MTCs [III, C]
- There is little evidence to support the use of either ChT or radionuclide therapy in patients with MTC, although either might be considered when MKIs are contraindicated

Filetti J. *Ann Onc*. 2019; 30: 1856.

Case Study

A Second Opinion

Second Opinion
Initial Presentation

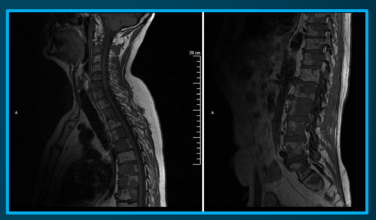
- 57-y-old man with metastatic medullary thyroid carcinoma (MTC) presented for second opinion in October 2018
- Patient presents with right neck mass in May 2018
- Final needle aspiration (FNA): MTC
- June 2018: total thyroidectomy, bilateral/central & upper mediastinal neck dissection
  - Pathology: MTC with extensive intrathyroidal spread, angioinvasion, & extrathyroidal spread; multifocal + margins; 30/66 + nodes on right, 15/45 + nodes on left
- Metastatic workup revealed liver lesions, + for MTC on FNA
- Foundation One Next Generation Sequencing (NGS): *RET* M918T, *CCDCN1,* & fibroblast growth factor receptor (FGFR) amplification

Case Study (continued)

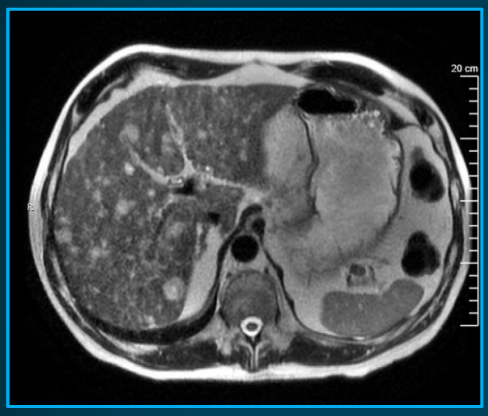
- Enrolled in a clinical trial investigating ipilimumab/nivolumab in thyroid cancers at an outside hospital (OSH)
- One dose, July 2018 → autoimmune hepatitis & pancreatitis
- Brain MRI July 2018: left cavernous sinus mass, treated with stereotactic body radiation therapy (SBRT)
- August 2018: cabozantinib 60 mg every day started
- October 2018 restaging: progressive disease (PD) in thoracic spine & liver
- Rising calcitonin: 101 (August 2018) → 276 (October 2018)

Case Study (2nd Opinion at Our Center)

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) = 1
- Labs: Grade 3 transaminitis, Grade 2 hyperbilirubinemia
- Ineligible for LIBRETTO-001 (LOXO-292) or ARROW (BLU-667)
- Single patient protocol through Loxo Oncology & US Food and Drug Administration (FDA)
- Ruled out germline *RET*
- Condition rapidly declined:
  - Nausea/vomiting, encephalopathic, ECOG PS = 4
- Started LOXO-292 at 80 mg twice a day
  - 50% of recommended phase 2 dose (RP2D) on *November 21, 2018*



Baseline Studies – November 2018



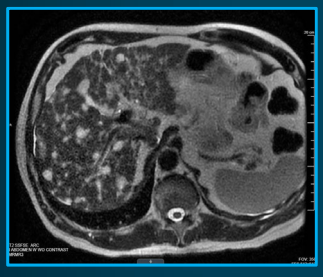
	11/18
CT	434
CEA	135.2

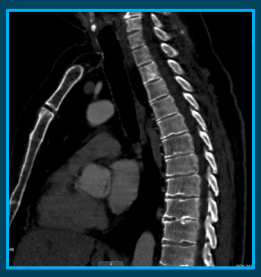
Widespread, innumerable peripherally enhancing lesions infiltrating liver

CT = calcitonin; CEA = carcinoembryonic antigen.

Case Study

- After 1 month, liver function tests (LFTs) improved to ≤ Grade 1; LOXO-292 increased to 120 mg twice a day
- Restaging after 2 cycles, January 2019:





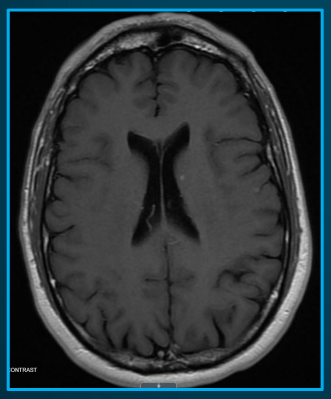
	11/18	1/19
CT	434	<5
CEA	135.2	1.6

Some liver lesions smaller, -15% by RECIST; bone lesions diffusely more sclerotic

RECIST = Response Evaluation Criteria in Solid Tumours.

Case Study

- Ongoing improvement in clinical status, imaging (partial response [PR] by RECIST) & tumor markers lasting 17 months, until April 2020

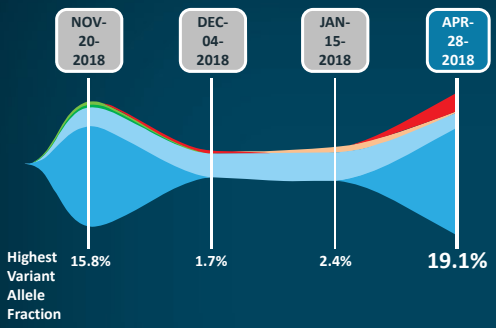


>15 new tiny enhancing supra- & infra-tentorial lesions; liver/bone metastases stable

	11/18	1/19	4/20
CT	434	<5	146
CEA	135.2	1.6	164.0

- LOXO-292 dosage increased to 240 mg twice a day
- Guardant360 CDx sent

Guardant360 CDx



Alteration	Associated FDA-Approved Therapies	Clinical Trial Availability	% CFDNA or Amplification
RET M918T	Cabozantinib, Selpercatinib, Vandetanib; Lenvatinib, Nintedanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib	Yes	19.1%
CCND1 Amplification	Abemaciclib, Palbociclib, Ribociclib	Yes	High (+++) Plasma Copy Number: 4.2
EGFR Amplification	Afatinib, Cetuximab, Neratinib, Panitumumab	Yes	Low (+) Plasma Copy Number: 2.3
CCNE1 Amplification	None	Yes	Low (+) Plasma Copy Number: 2.3
GATA3 T327fs	None	No	2.1%
CCNE1 D50E	None (VUS)§	No (VUS)§	0.1%

CFDNA = cell-free DNA.

Case Study

- Further central nervous system (CNS) progression on LOXO-292 240 mg twice a day
- Underwent whole brain radiation therapy (WBRT)
- Screening for enrollment in TPX-0046 ph 1/2 trial

TPX-0046 - Novel, Highly Potent RET/SRC Inhibitor

TPX-0046	
Differentiation	• Comparable potency against wild-type (WT) *RET* to proxy chemical compounds of other investigational *RET* agents • Only drug candidate with reported potency against the *RET* solvent-front mutation G810R
Target Population	• Advanced solid tumors with abnormal *RET* genes • TKI-naïve & pretreated
Development Stage	• Initiated Phase 1/2 study in November 2019

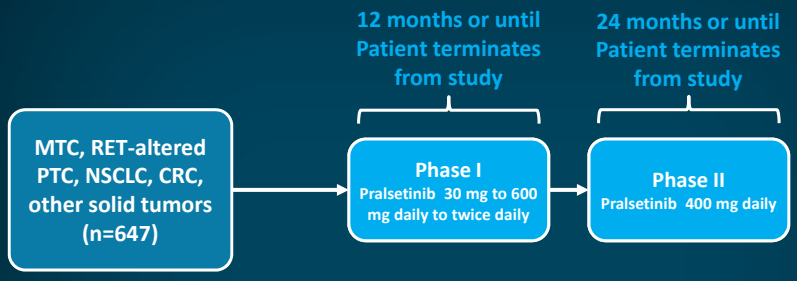
	Enzymatic Kinase Activity at 10 µM ATPIC IC_{50} (nM)[1]					Cell Proliferation IC_{50} (nM)[1]			
Inhibitor	***RET***	***RET*-CCDC6**	***RET* M918T**	**SRC**	**VEGFR2**	**Ba/F3 KIF5B-*RET* WT**	**Ba/F3 KIF5B-*RET* G810R** (solvent front mutation)	**Ba/F3 KIF5B-*RET* G810S** (solvent front mutation)	**Ba/F3 KIF5B-*RET* V804M** (gatekeeper mutation)
TPX-0046	**1.0**	**0.5**	**0.3**	**1.0**	**>1000**	**0.4**	**16.9**	**0.4**	**533**
BLU-667[2]	1.7	0.8	0.5	NR	NR	0.7	749	4.9	1.1
LOXO-292[2]	1.9	0.9	0.4	NR	NR	0.2	568	62.8	23.4

NR: Not reported.
1. All of the compounds were tested on the same plates in multiple experiments, & the data represent an average of the results.
2. Data based on evaluation of corresponding proxy chemical compound purchased from a commercial source rather than from the pharmaceutical company commercializing or developing the kinase inhibitor.

NCT04161391

Ongoing Development of RET Inhibitors

ARROW: Phase I/II, Open Label, First-In-Human



Key eligibility criteria

- Definitively diagnosed non-resectable advanced solid tumor
- Oncogenic RET-rearrangement/fusion or mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumor, except for MTC pts
- PS 0 - 1

- Phase 1 - Determination of maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of pralsetinib
- Phase 2 - Overall response rate
  Time Frame: Approximately every 8 weeks or 16 weeks based on the treatment cycle

Clinicaltrials.gov. NCT NCT03037385.

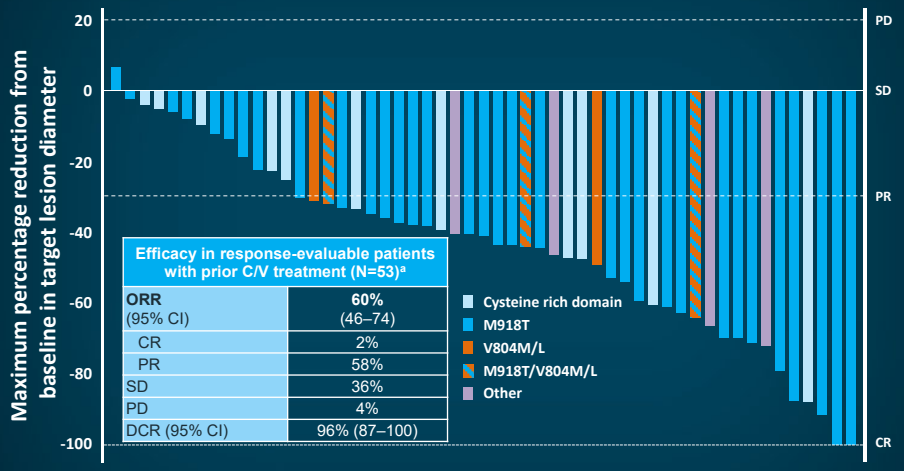
ARROW: Phase 1/2 Trial of Pralsetinib

- Pralsetinib (BLU-667) in patients with advanced RET mutation-positive MTC

Characteristic	All 400 mg pralsetinib (N=92)[a]	Prior cabozantinib and/or vandetanib treatment (n=61)	No prior systemic treatment (n=22)
Median age (range), years	59 (19–83)	58 (25–83)	60 (19–81)
Male, n (%)	63 (68)	41 (67)	16 (73)
ECOG PS, n (%)			
0	37 (40)	17 (28)	15 (68)
1–2[b]	55 (60)	44 (72)	7 (32)
History of CNS/brain metastases, n (%)	9 (10)	5 (8)	3 (14)
***RET* mutation**	92 (100)	61 (100)	22 (100)
M918T	56 (61)	41 (67)[c]	8 (36)
Cysteine rich domain[d]	27 (29)	14 (23)	11 (50)
V804M/L	3 (3)	2 (3)	1 (5)
Other[e]	6 (7)	4 (7)	2 (9)

Hu, et al., *ESMO*, 2020

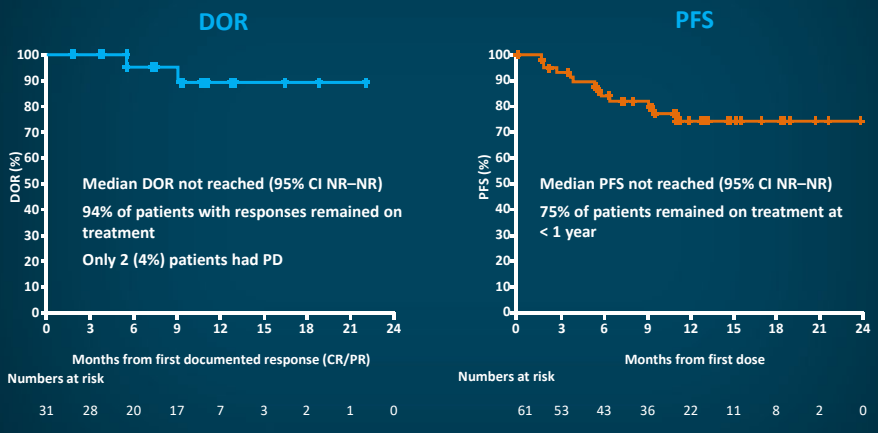
Clinical Response to Pralsetinib in Patients With Prior Cabozantinib and/or Vandetanib Treatment



aBlinded 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. b1

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.

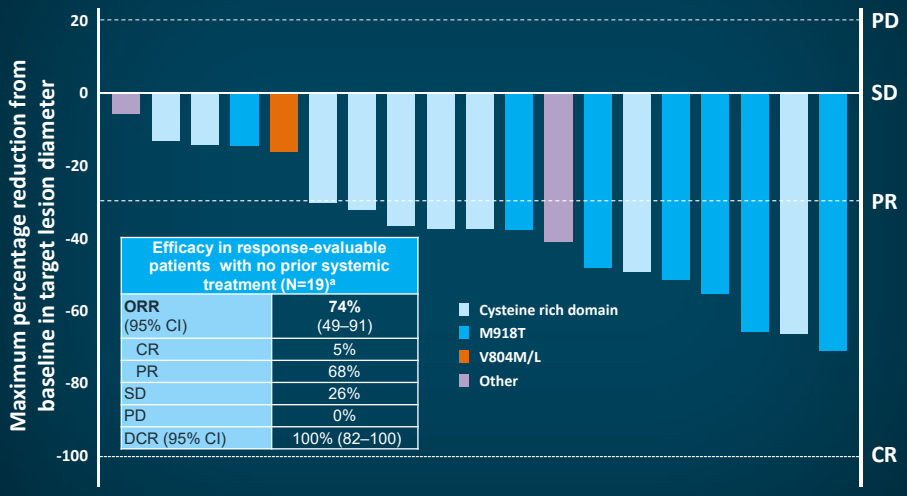
DOR and PFS with Pralsetinib In Patients With Prior Cabozantinib and/or Vandetanib Treatment



Blinded independent central review of tumor response; Patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020.

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

Clinical Response to Pralsetinib In Patients With No Prior Systemic Treatment



Efficacy in response-evaluable patients with no prior systemic treatment (N=19)[a]	
ORR (95% CI)	**74%** (49–91)
CR	5%
PR	68%
SD	26%
PD	0%
DCR (95% CI)	100% (82–100)

aBlinded independent central review of tumor response; response-evaluable patients enrolled by July 11, 2019, as of a data cut-off February 13, 2020. Two patients without measurable disease at baseline on central review and 1 patient who experienced major protocol violation were not response evaluable.

Pralsetinib Safety Profile (All Tumor Types)

TRAEs in ≥15% of patients	Pralsetinib 400 mg QD (N=438)	
	All grades	Grade ≥3
Aspartate aminotransferase increased	34%	2%
Anemia	24%	8%
Alanine aminotransferase increased	23%	2%
Hypertension	22%	11%
Constipation	23%	1%
White blood cell count decreased	18%	3%
Neutropenia	18%	10%
Neutrophil count decreased	16%	6%
Hyperphosphatemia	15%	1%

- Pralsetinib was well tolerated
- TRAEs were primarily Grade 1–2 and reversible
- 4% of patients discontinued due to TRAEs
- Median dose intensity was 92% (range 18–100)

Data cut-off February 13, 2020. TRAE, treatment-related adverse event.

Conclusions

- *RET* gene-specific therapy, i.e. selpercatinib and pralsetinib, in *RET*-mutant MTC exhibits potent and durable activity
  - Response rates range from 60% to 74%
  - Median DOR and PFS not yet reached in both LIBRETTO-001 and ARROW
- Activity across *RET* mutations, including gatekeeper resistance mut *RET* V804
- Activity similarly robust in *RET* fusion-positive thyroid cancer, including ATC
- Tolerability as expected with *RET*-specific drug design
- Selpercatinib PROs indicate stable to improved QoL, including in GI symptoms
- Acquired resistance on selpercatinib and pralsetinib has emerged
- Next generation *RET* specific clinical trials already underway

Many thanks, & best wishes for good health, safety and peace to all.

Questions and Answers

Precision Medicine: RET-Targeted Thyroid Carcinoma

Resource	Address
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Treatment of RET-driven Thyroid Carcinomas

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Dora Dias-Santagata, Jochen K. Lennerz. Response to RET-Specific Therapy in RET Fusion-Positive Anaplastic Thyroid Carcinoma. Thyroid. 2020;00. DOI: 10.1089/thy.2019.0477	https://pubmed.ncbi.nlm.nih.gov/32292131/
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