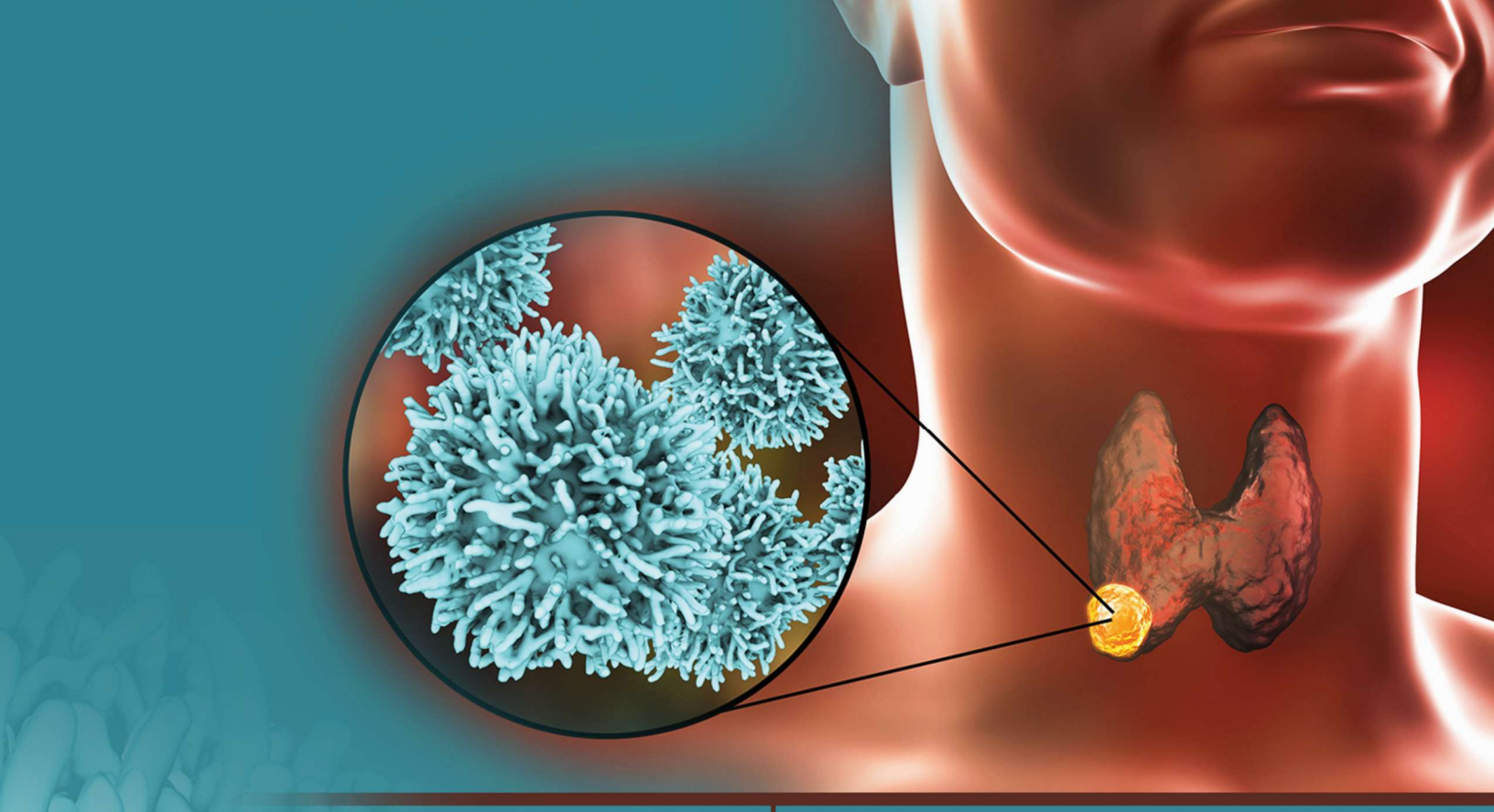

Project ECHO®

ECHO SERIES

Precision Medicine in Action:

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

MONDAY, DECEMBER 7, 2020

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Massachusetts General Hospital
Associate Professor of Medicine
Harvard University Medical School
Boston, MA

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Lilly.

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

FACULTY

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PROGRAM OVERVIEW
This case-based live virtual activity will cover the treatment and management of patients with 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/emerging less commonly occurring genomic alterations, genomic testing methodologies, and optimal treatment decisions for patients with thyroid cancer.

LEARNING OBJECTIVES
- 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

ACCREDITATION STATEMENT
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CREDIT DESIGNATION STATEMENT
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NURSING CREDIT INFORMATION
Purpose: This program would be beneficial for nurses involved in the care of patients with thyroid cancer.
CNE Credits: 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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Lori Wirth, MD has received honorarium for advisory roles from:

- Ayala Pharmaceuticals
- Bayer Healthcare Pharmaceuticals (consulting fees)
- Blueprint Medicines (consulting fees)
- Cue BioPharma (consulting fees)
- Cullinan Oncology
- Eli Lilly (consulting fees)
- Eisai (consulting fees)
- Genentech USA
- Merck (consulting fees)
- Loxo Oncology (consulting fees)
- NewLink Genetics
- Novartis
- Rakuten Medical
- Honoraria received for serving on a steering committee for Eli Lilly
- Honoraria received for serving on a data safety monitoring board for Lovance Biotherapeutics

CME Content Review

The content of this activity was independently peer-reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer-reviewed by a nurse reviewer.
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- Christina Gallo, SVP, Educational Development of Med Learning Group, has nothing to disclose.
- Ana Maria Albino, Senior Program Manager of Med Learning Group, has nothing to disclose.
- David Chatman, Medical Director of Med Learning Group, has nothing to disclose.
- Lauren Welch, MA, VP of Accreditation and Outcomes of Med Learning Group, has nothing to disclose.
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There are no fees for participating and receiving CME/CE credit for this live virtual activity. To receive CME/CE credit participants must:

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

You will receive your certificate upon completion as a downloadable file.

DISCLAIMER

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PROGAM AGENDA

I. **Thyroid cancer overview**
   a. Epidemiology
   b. Histological subtypes
   c. Pathophysiology and disease course
   d. Traditional standard of care therapies for advanced thyroid cancer
   e. Advantages and disadvantages associated with the traditional watch and wait approach

II. **Molecular/Genomic alterations associated with thyroid cancer**
   a. RET mutations as an example
   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 the integration of routine molecular/genomic testing into clinical practice

III. **Applying precision medicine approaches to the treatment of patients with advanced thyroid cancer**
   a. Available targeted therapeutic options for patients with advanced 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

IV. **Conclusion and questions and answers**

Posting Questions in Zoom Chat

- If you would like to post a question during the presentation, please submit your inquiry in the chat feature.
- Remember to direct all questions to the “co-host.” There is a toggle button above the typing space that allows you to specify the location of your message delivery.

1

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

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Educational Objectives

- 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 of patients with advanced thyroid cancer based on results showing actionable molecular/genomic alterations

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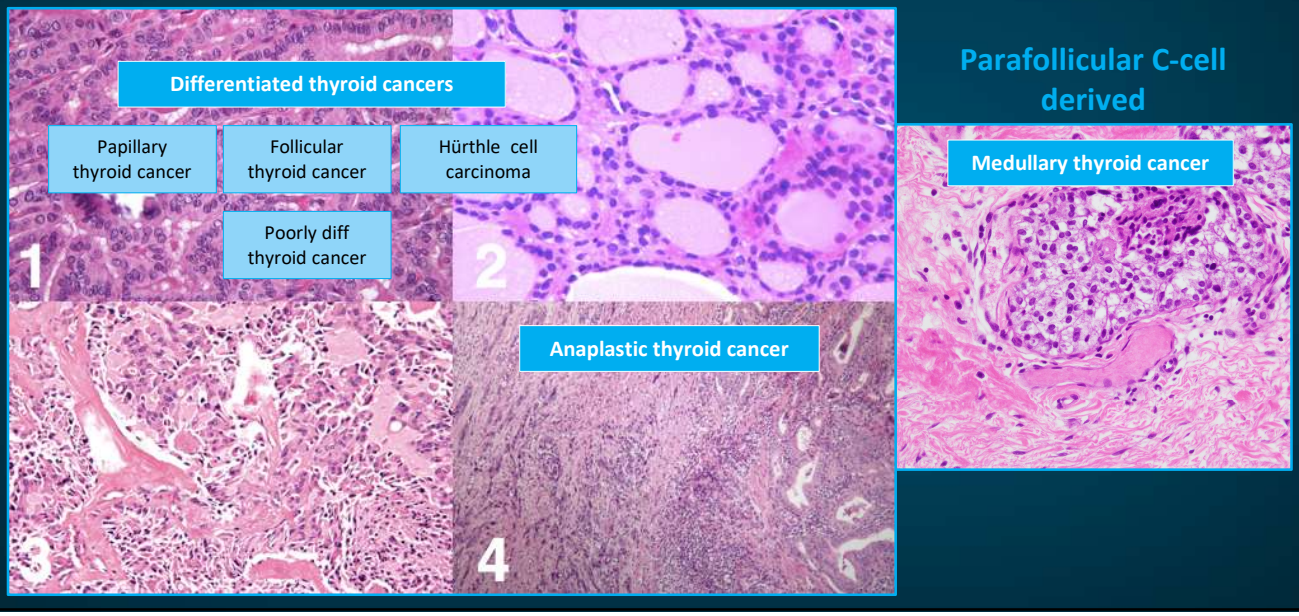
The Array of Thyroid Cancers



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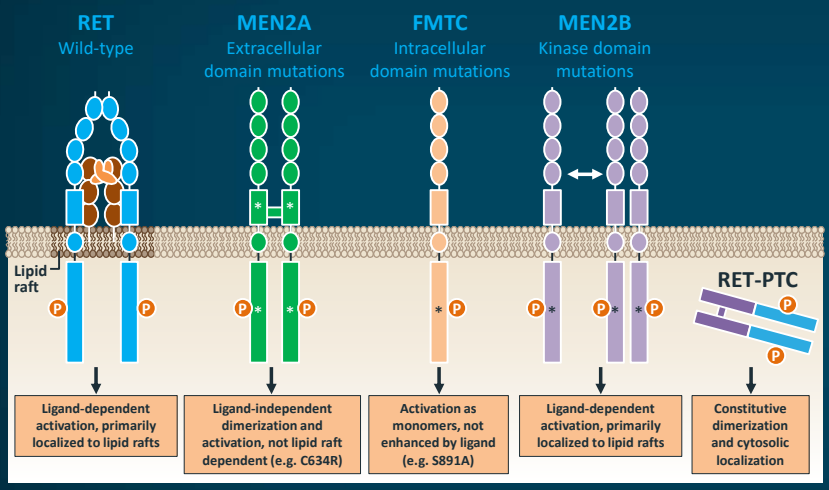
RET Proto-Oncogene

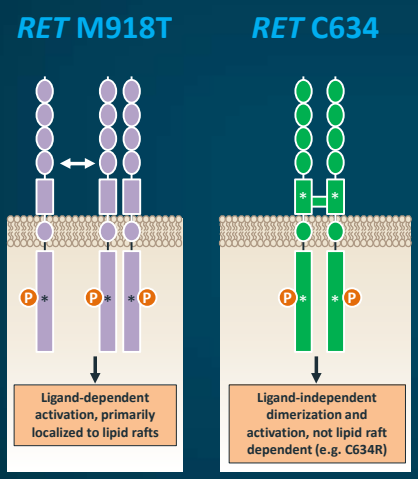


- *RET* proto-oncogene encodes transmembrane receptor tyrosine kinase
- Activated in thyroid cancer via 2 distinct mechanisms:
- *RET* mutations in cysteine-rich extracellular or kinase domains
- Gene rearrangement → fusion of *RET* to 5' upstream partner
- Both → ligand-independent signaling & oncogenesis

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

6

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



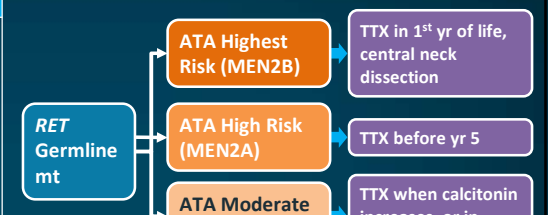
- *RET* mutations drive 60% of MTCs
- 20% of MTC are hereditary – all patients have germline *RET* mutations
- 50% of sporadic MTCs harbor somatic *RET* mutations
- *RET* M918T most common somatic mutation
- Germline *RET* M918T occurs in nearly all MEN 2B patients
- Germline *RET* C634 most common hereditary mutation (MEN 2A)
- *RET* C634 can also occur somatically

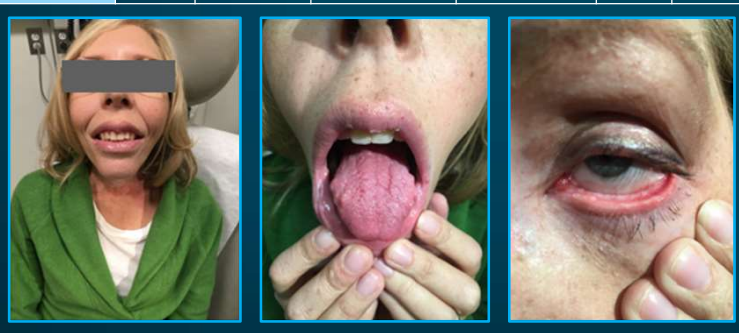
Ciampi, et al. *iScience*, 2019; Mulligan, *Nature Rev Cancer*, 2014

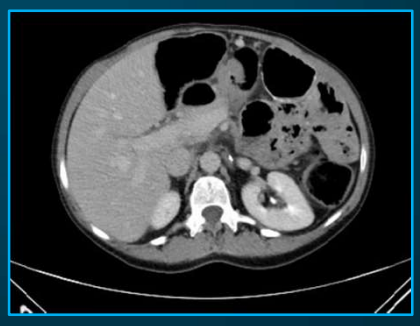
7

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





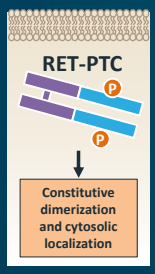


Phay, *Semin Surg Oncol*, 2000; Wells, *Thyroid*, 2015

8

RET Fusion-Driven Thyroid Cancer

CCDC6-RET



- *RET* fusions in < 10% of papillary thyroid cancers (PTCs)
- Seen less commonly in poorly differentiated and anaplastic thyroid cancers
- More frequent in pediatric and young adult PTCs, ~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

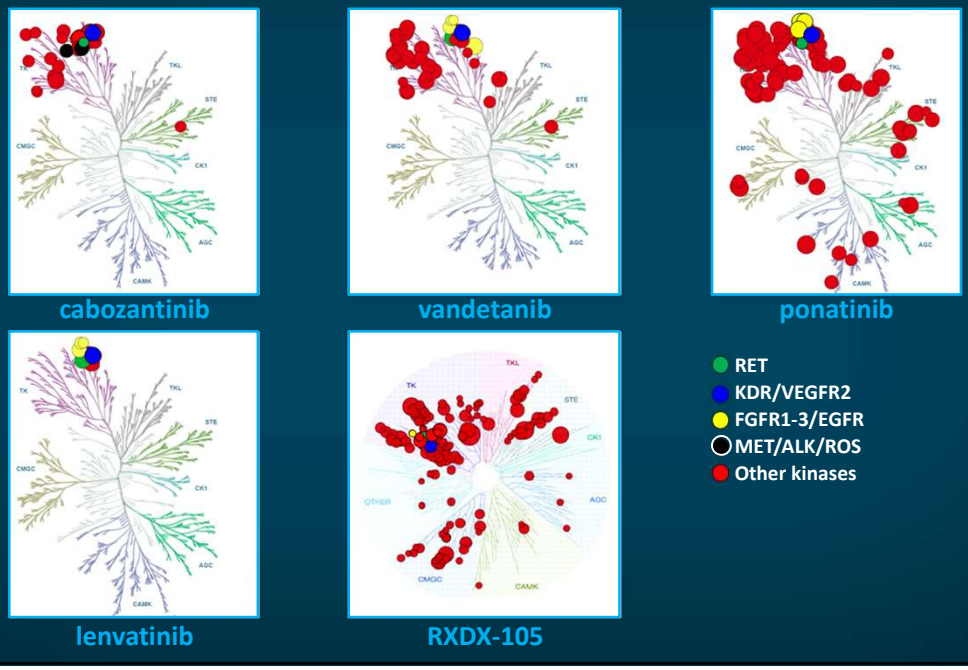
9

RET-targeted Therapy

Lori Wirth, MD

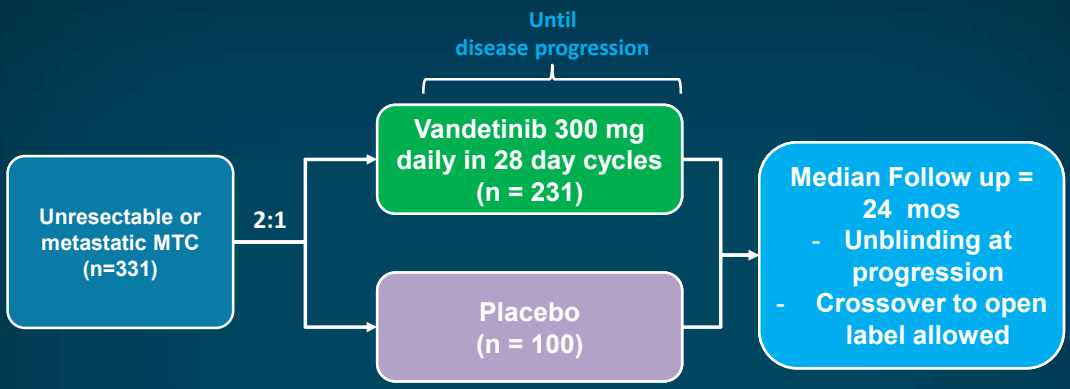
10

Kinome Selectivity For MKIs With RET Activity



11

Vandetinib in Metastatic Medullary Thyroid Cancer



Key eligibility criteria

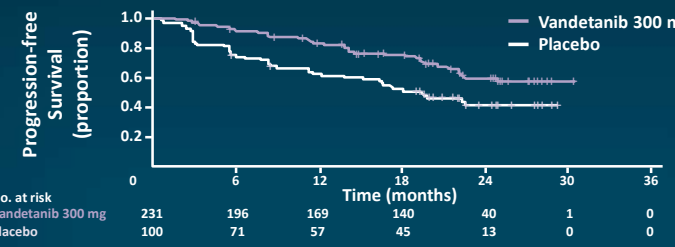
- RECIST-measurable disease
- PS 0-2
- Serum calcitonin ≥ 500 pg/mL
- No more than one prior therapy with a TKI

- 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

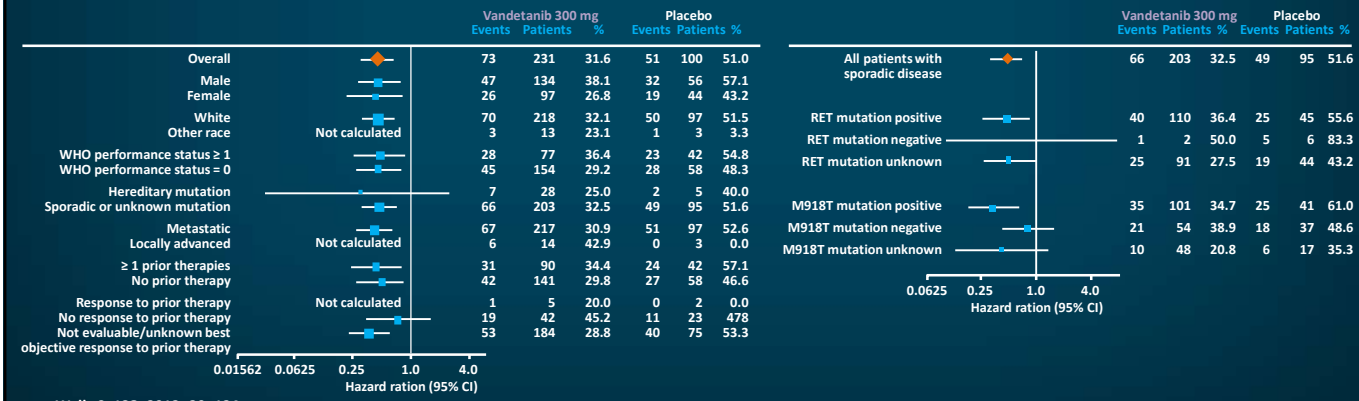
Wells S. *JCO*. 2012; 30: 134.

12

Vandetanib Results in MTC



Med PFS_{van} not reached *v.* Med PFS_{plac} 19.3 mos
(HR, 0.46; 95% CI, 0.31 to 0.69; $p < .001$)



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

13

Vandetanib – Safety and Tolerability in MTC

Common Adverse Events (safety population)

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

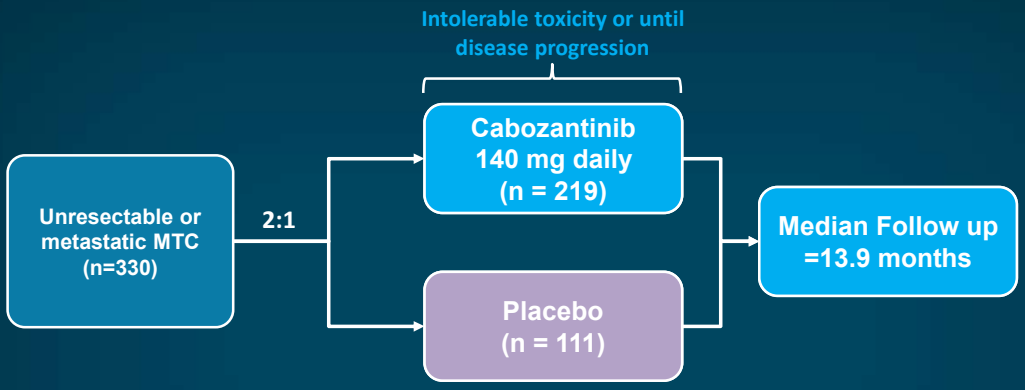
Prolonged QTc – vandetanib is only available through REMS program.

*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.

14

Cabozantinib in Progressive, Metastatic MTC



Key eligibility criteria

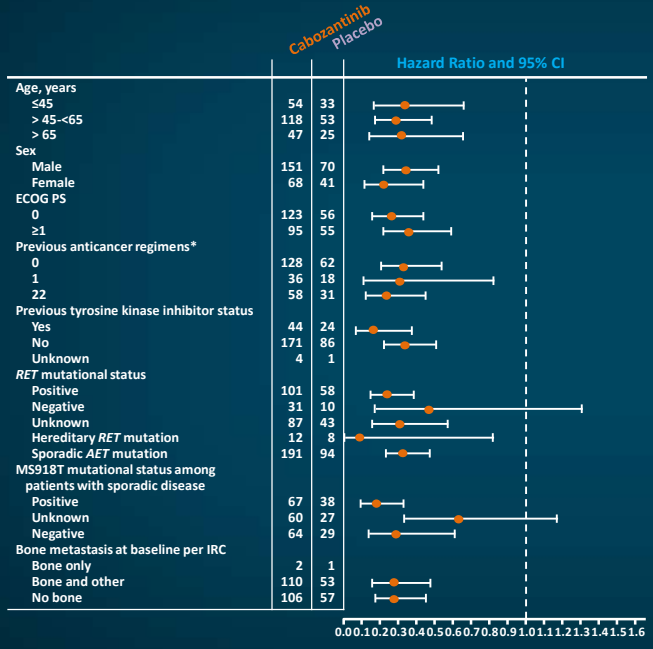
- Definitively diagnosed non-resectable
- RECIST-measurable progressive disease
- No restriction on prior therapy, including other TKIs

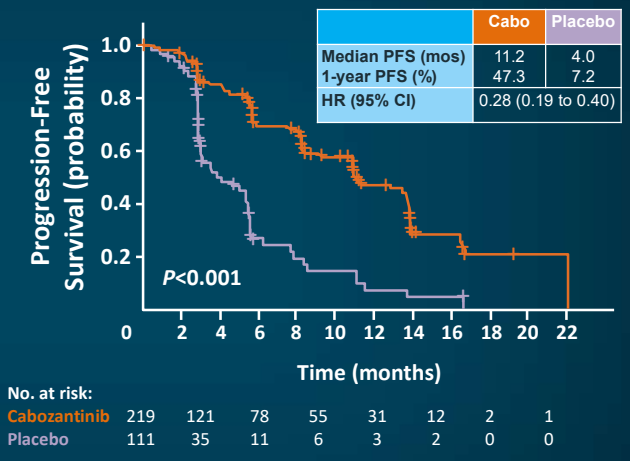
- Primary endpoint – progression free survival (PFS)
- Secondary endpoints – tumor response rate, overall survival (OS), overall response rate (ORR), and safety
- RET mutation positive = 49.2% and negative = 12%
- RET status unknown = 39%

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

15

Progression Free Survival Analysis





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

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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	—

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

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

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

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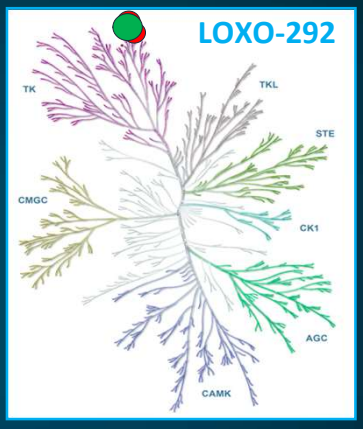
Honing in on RET



- 2 new highly potent and specific RET inhibitors completed first-in-human trials
  - Selpercatinib (LOXO-292)
  - Pralsetinib (BLU-667)
- Both designed to potently inhibit
  - wildtype RET in fusions (in PTC, NSCLC, etc)
  - Oncogenic RET mutations (in MTC)
  - And V804 acquired gatekeeper mut, 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

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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*-mutant MTC, previously treated with vandetinib +/or cabozantinib
  - *RET*-mutant 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.

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Patient Characteristics

- *RET*-mutant MTC, previously treated: n = 55
  - 60% *RET* M918T
  - 13% extracellular cysteine-rich domain mt
  - Familial and sporadic patients enrolled
- *RET*-mutant 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.

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)

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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

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)

d/t = due to . TRAE = treatment-related adverse events.

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

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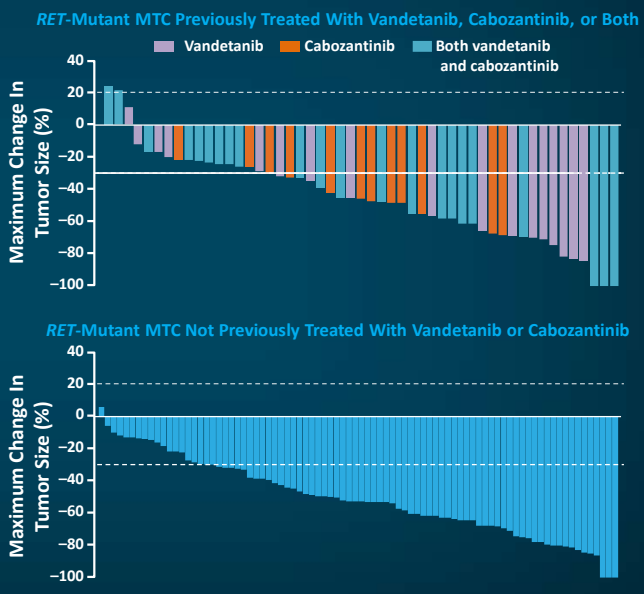
Selpercatinib Efficacy in MTC

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

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



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

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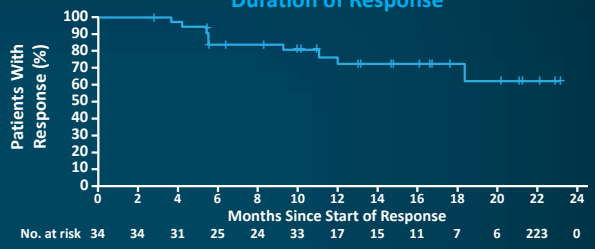
Selpercatinib Efficacy in MTC

Duration of response & progression-free survival

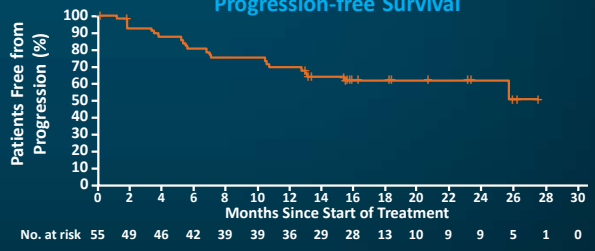
- Median DOR not yet reached
  - (95% CI, 19.1 mos to NE)
  - Median follow-up = 14.1 mos
- Median PFS not yet reached
  - Median follow-up = 16.7 mos
  - (95% CI, 24.4 mos to NE)

RET-Mutant MTC Previously Treated With Vandetanib, Cabozantinib, or Both

Duration of Response



Progression-free Survival




U.S. FOOD & DRUG ADMINISTRATION

FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions

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

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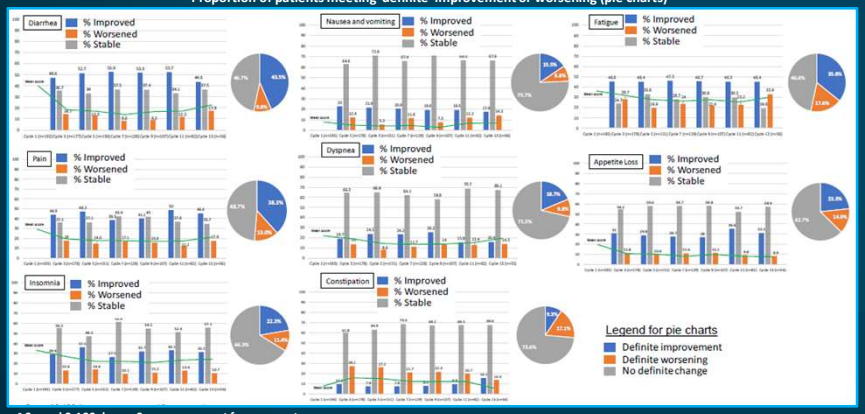
LIBRETTO-001 Patient-Reported Outcomes in MTC

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

Symptom subscales (QLQ-C30)[a]

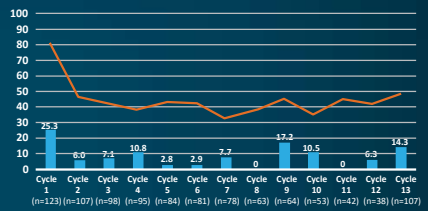
Mean scores and proportion of patients meeting a clinically meaningful difference (CMD) by cycle of therapy (bar and line graphs)[b]
Proportion of patients meeting 'definite' improvement or worsening (pie charts)[c]



[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.

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

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, frequent 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

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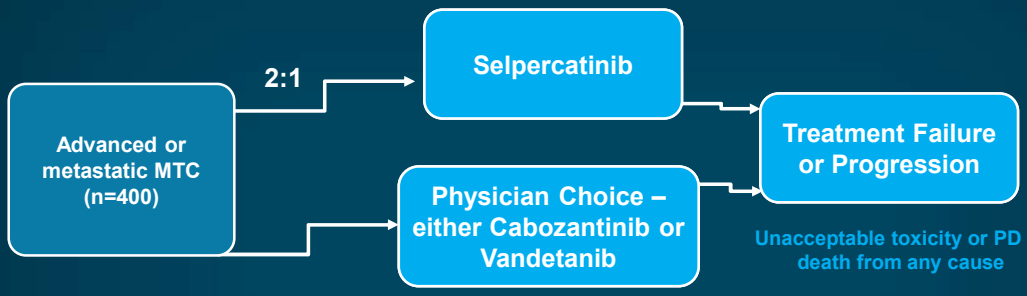
Future Directions with Selpercatinib in MTC

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.

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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

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Case Study
History of breast cancer

Lori Wirth, MD

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Case Study

- 59-yr-old woman with a history of breast cancer was found to have an elevated carcinoembryogenic antigen (CEA) of 456 ng/dl during a routine follow up visit.
- Her PMH is significant for atherosclerotic heart disease and HTN
- She had no specific complaints and presented with no signs or symptoms.
- PET/CT was performed with a left thyroid lobe uptake and metabolically active lymphadenopathy, bilaterally. CT scans of neck, chest, abdomen and pelvis revealed extensive lymphadenopathy in neck and upper mediastinum and a 2.6 cm liver mass consistent with metastatic disease.
- FNA cytology confirmed medullary thyroid carcinoma

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Case Study (continued)

- A total thyroidectomy with central compartment and bilateral neck dissection is conducted
- Mutational testing was positive for RET mutation
- Calcitonin levels 7500 pg/dl preoperatively were reduced to 3400 pg/dl 3 months postoperatively

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Audience Polling Question

What are your possible treatment options?

A. Begin vandetanib
B. Begin selpercatinib
C. Begin cabozantinib
D. Follow serial calcitonin levels and begin systemic therapy when trending up from post-operative levels
E. A and B
F. B and C

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Case Study (continued)

- Patient begins on selpercatinib
- Monitor calcitonin and CEA every 3 months
- Three months after start of selpercatinib patient's calcitonin and CEA are WNL
- Patient's LFTs are WNL

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Discussion Question

Have you seen de novo resistance to RET targeted therapy?
If yes, when/how did you make that determination?
Confirmed with mutational testing?

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Case Presentation
23 yo with Childhood Diagnosis

Sylvia Asa, MD

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Case History

- 23-year-old white female
- History of MTC diagnosed at age 8 years
- Lymph node metastases present at that time
- Diffuse ganglioneuromatosis of the colon and appendix were also present
- Thyroidectomy and neck dissection

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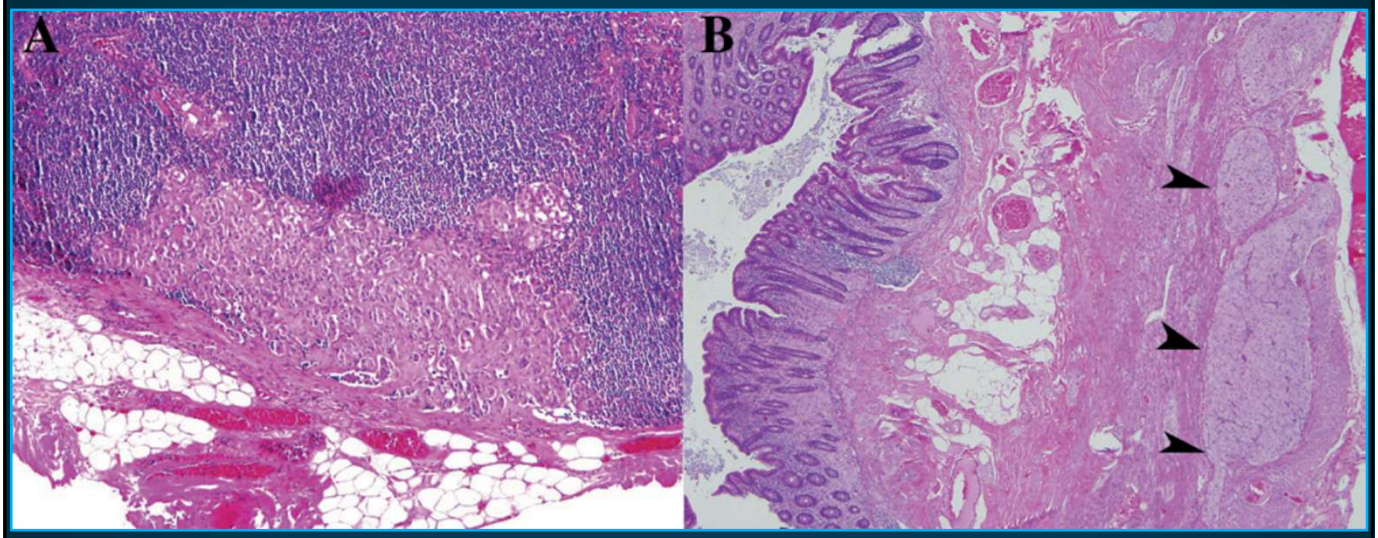
Histopathologic Findings



Metastatic MTC in Lymph node

Appendiceal ganglioneuromas

Williams MD et al: *Annals of Diagnostic Pathology* 12 (2008) 199– 203

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Discussion Question

What do findings such as ganglioneuromas indicate to you and how may that affect future monitoring?

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Case History

- Germ-line point mutation in RET consistent with MEN2b
- No family members with the mutation, a finding that is present in 50% of MEN2b cases

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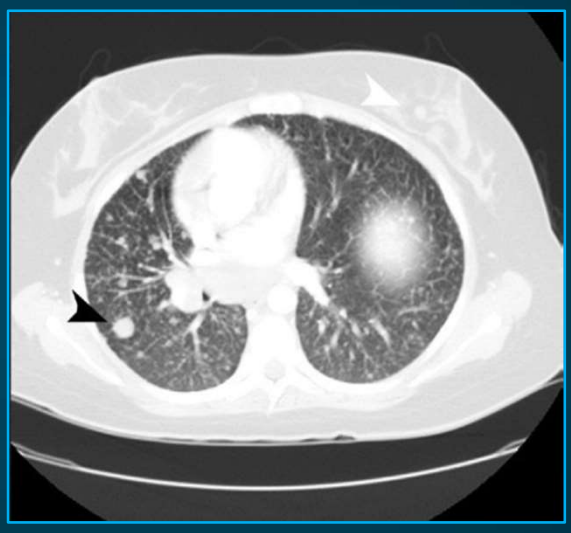
Case History (continued)

- No clinical evidence of metastatic disease for 15 years despite persistently elevated calcitonin levels
- Then: Lung metastasis



Williams MD et al: *Annals of Diagnostic Pathology* 12 (2008) 199– 203

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Polling Question

In a patient with a history similar to this case; RET-positive, MTC diagnosed in childhood, s/p thyroidectomy and neck dissection, with persistently elevated calcitonin levels what would be your recommendation upon initial diagnosis?

A. Monitor calcitonin and CEA levels every 6 – 12 months

B. Monitor calcitonin, CEA and conduct CT scans every 12 months

C. Although asymptomatic, begin systemic RET-targeted therapy and monitor calcitonin and CEA levels

D. All of the above

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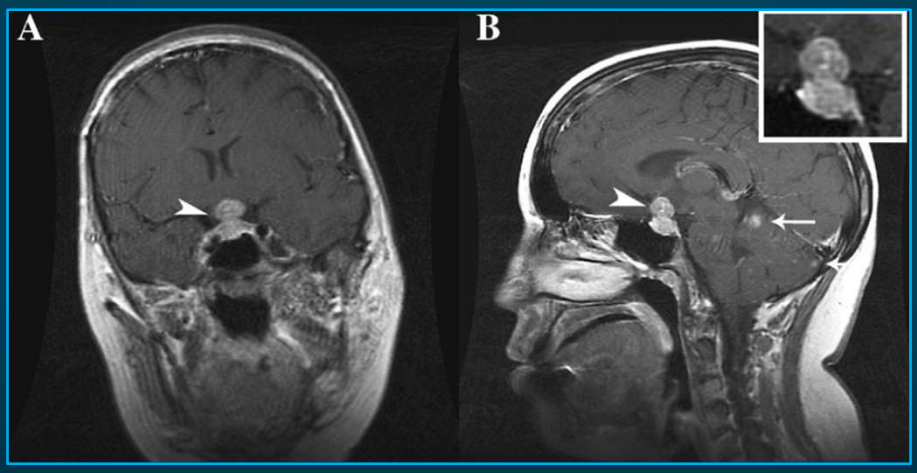
New Symptoms

- Polydipsia, polyurina, headaches, and lethargy c/w diabetes insipidus
- Visual exam: bitemporal hemianopsia



Williams MD et al: *Annals of Diagnostic Pathology* 12 (2008) 199– 203

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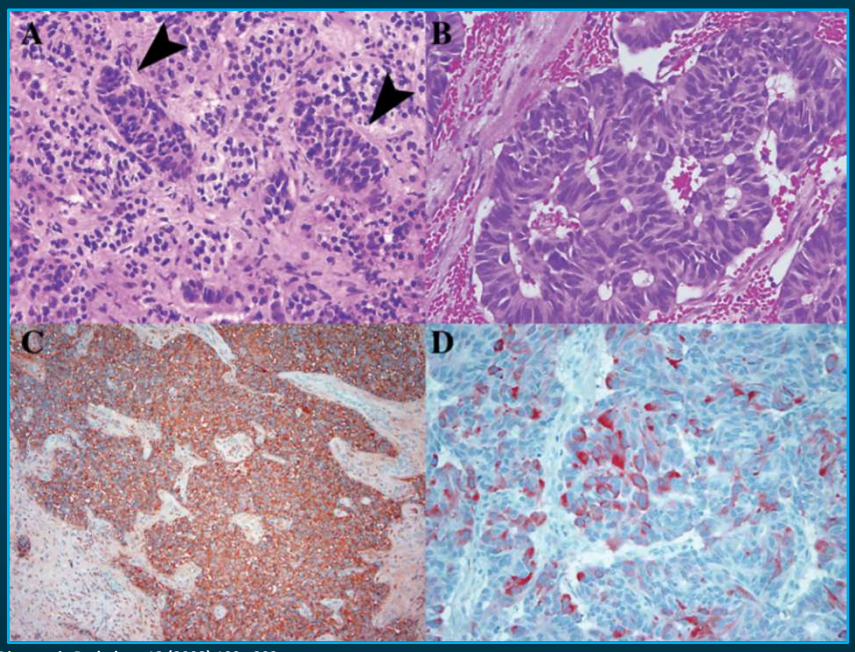
Pituitary Pathology: Metastatic MTC to Pituitary



Williams MD et al: *Annals of Diagnostic Pathology* 12 (2008) 199– 203

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Conclusions

- *RET* gene-specific therapy (ie, selpercatinib & pralsetinib) in *RET*-mutant MTC exhibits potent & durable activity
  - Response rates range from 60% to 74%
  - Median duration of response & PFS not yet reached in both LIBRETTO-001 & ARROW
  - Pralsetinib approved Dec 1, 2020 by FDA – adv/met RET-mutant & RET-fusion-positive thyroid cancer
- 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 patient-reported outcomes (PROs) indicate stable to improved quality of life (QoL), including in gastrointestinal (GI) symptoms
- Acquired resistance on selpercatinib & pralsetinib has emerged
- Next generation *RET*-specific clinical trials already underway

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

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Thank you!

Questions & Answers

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Thyroid Cancer Poster Portal

Project ECHO®

Med Learning Group - Thyroid Cancer

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