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Selpercatinib (LOXO-292) in Patients with *RET*-altered Thyroid Cancers

Manisha H. Shah[1], Eric J. Sherman[2], Bruce Robinson[3], Benjamin Solomon[4], Hyunseok Kang[5], Jochen H. Lorch[6], Francis Worden[7], Marcia S. Brose[8], Sophie Leboulleux[9], Yann Godbert[10], Marie Meurer[11], John Morris[12], Taofeek K. Owonikoko[13], Daniel Shao-Weng Tan[14], Oliver Gautschi[15], Jyoti Patel[16], Luxi Yang[17], Jennifer Kherani[17], Maria E. Cabanillas[18], Lori J. Wirth[19]

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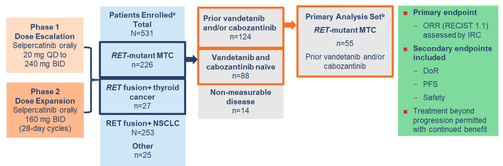
BACKGROUND

- Treatment options for *RET*-mutant medullary thyroid cancer (MTC) and differentiated thyroid cancers have been limited (e.g., highly toxic multikinase inhibitors [MKIs]).
- Selpercatinib (LOXO-292) is a highly selective and potent small molecule RET kinase inhibitor.
- In an ongoing, first in human, phase 1/2 trial, selpercatinib treatment in patients with *RET*-altered cancers demonstrated
  - Marked and durable investigator-assessed antitumor activity in patients with *RET*-mutant MTC, with or without prior vandetanib and/or cabozantinib therapy, and in patients with *RET* fusion+ thyroid cancer.
  - A tolerable safety profile.
- In May 2020, selpercatinib was approved by the US FDA under the Accelerated Approval program for the treatment of 3 types of *RET*-altered cancers:
  - *RET* fusion-positive NSCLC
  - *RET*-mutant MTC
  - *RET* fusion-positive thyroid cancers

OBJECTIVES

- Here we report an update on the efficacy, including tumor assessment by blinded independent review committee, and the safety of selpercatinib in patients with *RET*-mutant MTC or *RET* fusion+ thyroid cancer.

STUDY DESIGN



The Phase 1/2 LIBRETTO-001 Trial: Selpercatinib in Patients with *RET*-altered Cancers

- An ongoing global, multicenter trial (NCT03157128) conducted in 16 countries and 89 sites.
- [a]Number of patients enrolled and treated as of 17-Jun-2019. Data cutoff date: 16-Dec-2019.
- [b]The primary analysis set (PAS) was defined through health authority agreement as the first 55 consecutively enrolled patients with *RET*-mutant MTC previously treated with vandetanib and/or cabozantinib. Patients with non-measurable disease enrolled in Phase 1 dose escalation were included in the PAS.
- *RET* alteration determined by local CLIA or similarly accredited laboratories using next-generation sequencing, FISH, or PCR.
- **Key inclusion criteria:** Age of ≥18 years or ≥12 years if permitted by regulatory authorities, diagnosis of advanced or metastatic solid tumor, ECOG PS 0 to 2, QTc of ≤470 msec, and adequate organ function.

Abbreviations: BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IRC, independent review committee; MTC, medullary thyroid cancer; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PCR, polymerase chain reaction; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

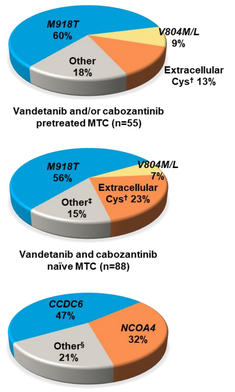
RESULTS

Baseline Patient Characteristics

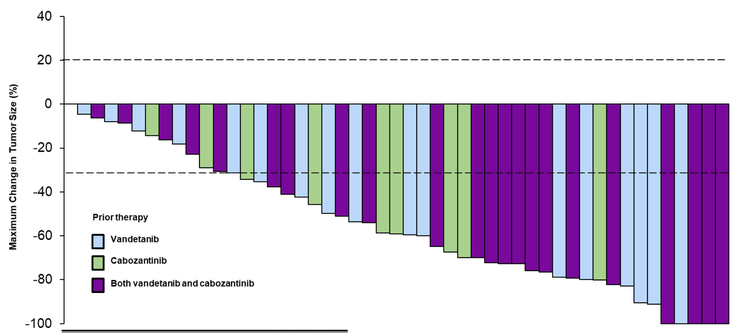
Characteristic n (%) unless otherwise stated	*RET*-mutant MTC Vande and/or Cabo Pretreated (n=55)	*RET*-mutant MTC Vande/Cabo Naive (n=88)	*RET* Fusion+ Thyroid Cancer (n=19)
Age, Median (range), year	57 (17–84)	58 (15–82)	54 (25–88)
Sex			
Male	36 (66)	58 (66)	9 (47)
Female	19 (35)	30 (34)	10 (53)
Race*			
White	49 (89)	75 (85)	14 (74)
Asian	0	4 (5)	2 (11)
Black or African American	1 (2)	1 (1)	1 (5)
Other	5 (9)	8 (9)	2 (11)
ECOG performance status			
0	11 (20)	43 (49)	5 (26)
1	41 (75)	42 (48)	12 (63)
2	3 (6)	3 (3)	2 (11)
Thyroid cancer tumor type			
Medullary	55 (100)	88 (100)	–
Papillary	–	–	13 (68)
Poorly differentiated	–	–	3 (16)
Hürthle cell	–	–	1 (5)
Anaplastic	–	–	2 (11)
Prior systemic regimens, median (range)	2 (1–8)	0 (0–2)	4 (1–7)
Prior vandetanib and/or cabozantinib**	55 (100)	–	–
Vandetanib only	18 (33)	–	–
Cabozantinib only	13 (24)	–	–
Vandetanib and cabozantinib	24 (44)	–	–
Prior radioactive iodine (RAI)**	–	–	16 (84)
Prior sorafenib and/or lenvatinib**	–	–	13 (68)
Prior multikinase inhibitor (MKI) therapy	55 (100)	7 (8)	15 (79)
1	26 (47)	6 (7)	7 (37)
≥2	29 (53)	1 (1)	8 (42)
Prior non-MKI therapy	17 (31)	9 (10)	14 (74)
Brain metastases	4 (7)	2 (2)	6 (32)

*Includes 1 *RET* fusion-positive patient with missing race. **Prior cancer treatments relevant to disease type are presented. [‡]Extracellular cysteine mutation defined as mutation including at least 1 of the following cysteine residues: 609, 611, 618, 620, 630, and 634. [§]Other includes: D631-L633delinsE, E632-L633del, A883F, D631-L633delinsV, L790F, D898-E901del, D898_E901del + D903_S904delinsEP, K666N, T636-V637insCRT, D378-G385delinsE. [¶]Fusions identified in single tumors included *CCDC186-RET*, *ERC1-RET*, *KTN1-RET*, and *RUFY3-RET*. Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating greater disability. Total % may be different than the sum of the individual components due to rounding. Abbreviations: Cabo, cabozantinib; Vande, vandetanib.

***RET* Alterations**



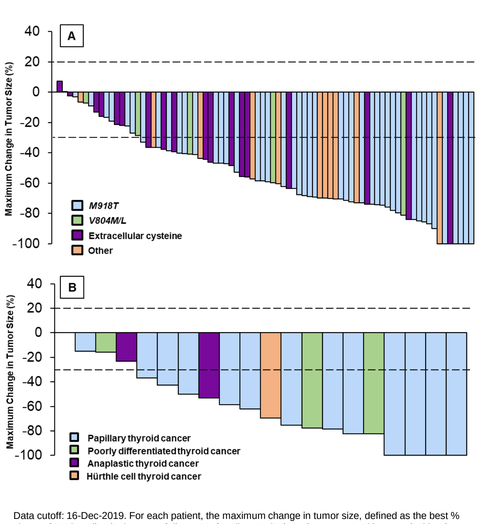
Marked Antitumor Activity with Selpercatinib in Patients with *RET*-mutant MTC Pretreated with Vandetanib and/or Cabozantinib, as Assessed by Independent Review Committee



	RET-mutant MTC Prior Vandetanib/Cabozantinib (n=55)
ORR by IRC, % (95% CI)	**69 (55–81)**
Best response by IRC, n (%)	
Complete response (CR)	5 (9)
Partial response (PR)	33 (60)
Stable disease (SD)	14 (26)
Progressive disease (PD)	1 (2)
Not evaluable (NE)	2 (4)

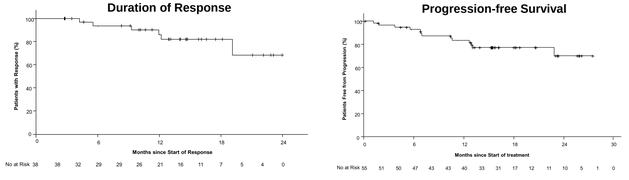
Data cutoff: 16-Dec-2019. For each patient, the maximum change in tumor size, defined as the best % change from baseline in the sum of diameters for all target lesions, is represented by a vertical bar in waterfall plot. 7 patients are not shown as 2 discontinued prior to post-baseline imaging assessments, and 5 had non-measurable disease at baseline. Abbreviations: IRC, independent review committee; ORR, objective response rate.

Marked Antitumor Activity with Selpercatinib in Patients with *RET*-mutant MTC Naïve to Vandetanib and Cabozantinib (A) and in Previously-Treated* Patients with *RET* Fusion+ Thyroid Cancer (B), as Assessed by Independent Review Committee



Data cutoff: 16-Dec-2019. For each patient, the maximum change in tumor size, defined as the best % change from baseline in the sum of diameters for all target lesions, is represented by a vertical bar in waterfall plot. (A) 8 patients are not shown as 2 discontinued prior to post-baseline imaging assessments, and 6 had non-measurable disease at baseline. (B) All patients shown. *Prior systemic regimens, median (range): 4 (1–7).

Selpercatinib Benefit in Prior Vandetanib and/or Cabozantinib-treated Patients with *RET*-mutant MTC, as Assessed by Independent Review Committee



Selpercatinib Benefit in all Thyroid Cancer Treatment Groups as Assessed by Independent Review Committee and Investigators

	RET-mutant MTC Vandetanib and/or Cabozantinib Pretreated		*RET*-mutant MTC Vandetanib and Cabozantinib Naive		Previously-Treated *RET* Fusion+ 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 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)	20 (9–NE)	NE (10–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 (37–82)	61 (33–81)

*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.

Biochemical Response in Patients with *RET*-mutant MTC Pretreated with Vandetanib and/or Cabozantinib

	Calcitonin (n=54)	CEA (n=53)
ORR, % (95% CI)	**91 (80-97)**	**66 (52-79)**
Best response, n (%)		
Complete response (CR)	14 (26)	8 (15)
Partial response (PR)	35 (65)	27 (51)
Stable disease (SD)	0	9 (17)
Progressive disease (PD)	1 (2)	7 (13)
Not evaluable (NE)	4 (7)	2 (4)

Data cutoff: 16-Dec-2019. For patients with *RET*-mutant MTC pretreated with vandetanib and/or cabozantinib, serum calcitonin and carcinoembryonic antigen (CEA) levels were followed longitudinally. Best biochemical response for serum calcitonin and CEA was defined as follows: complete response, normalization of serum levels; partial response, ≥ 50% decrease from baseline levels; stable disease, if <50% decrease or increase from baseline; and progression if ≥50% increase from baseline (each maintained for at least 4 weeks). Abbreviation: ORR, objective response rate.

Selpercatinib Overcomes Germline *RET V804M* Gatekeeper Mutation (images in scannable slide deck)

- 56-year-old man with hereditary *RET* V804M-mutant MTC
- Massive metastatic infiltration of the liver
- 3 prior anti-*RET* MKIs: cabozantinib, vandetanib, lenvatinib
- Initiated selpercatinib at 80 mg BID with escalation to 160 mg BID
- Rapid reduction in serum CEA and calcitonin, resolution of diarrhea, abdominal distension, and abdominal pain
- Confirmed CR by RECIST 1.1 after 8 weeks of treatment
- Remains on treatment at 25 months

Selpercatinib Activity in *CCDC6-RET* Fusion+ Anaplastic Thyroid Cancer (images in scannable slide deck)

- 73-year-old man with *CCDC6-RET* fusion+ anaplastic thyroid cancer
- Metastatic disease to lungs and brain*
- Previous surgery, SRS, and docetaxel/doxorubicin
- Initiated selpercatinib at 160 mg BID
- Confirmed PR by RECIST 1.1 after 8 weeks of treatment
- Remains on treatment at 19 months

Adverse Events in all Selpercatinib-treated Patients (N=531)*

Adverse Event, %	Adverse Event, Regardless of Attribution					Treatment-related Adverse Event		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
Diarrhea	27	9	4	–	40	2	–	22
Dry mouth	33	5	–	–	38	–	–	33
Hypertension	4	14	17	<1	36	11	<1	24
Aspartate aminotransferase increased	19	6	7	1	32	5	1	26
Fatigue	18	11	1	–	30	<1	–	18
Alanine aminotransferase increased	15	5	9	1	30	7	1	25
Nausea	21	6	1	–	27	<1	–	11
Constipation	21	5	1	–	27	<1	–	12
Edema peripheral	22	4	<1	–	27	–	–	15
Headache	18	5	2	–	24	<1	–	8
Blood creatinine increased	15	5	–	<1	21	–	–	11
Abdominal pain	14	5	2	–	20	<1	–	5
Rash	15	3	1	–	19	1	–	12
Vomiting	14	4	<1	–	18	<1	–	5
Cough	14	2	–	–	16	–	–	1
Electrocardiogram QT prolonged	5	7	4	–	16	3	–	12
Dyspnea	10	3	2	<1	16	–	–	1

Data cutoff: 16-Dec-2019. *The adverse events (AEs) listed here are those that occurred at any grade in at least 15% of patients, regardless of attribution. The relatedness of AEs to treatment was determined by the investigators. Total % for any given AE may be different than the sum of the individual grades, due to rounding. In total, 19 patients experienced grade 5 AEs including cardiac arrest (3), sepsis (3), respiratory failure (2), brain herniation, cardiac failure, cerebral hemorrhage, cerebrovascular accident, general physical health deterioration, hemoptysis, hypoxia, multiple organ dysfunction syndrome, neoplasm progression, pneumonia, and post-procedure hemorrhage (one each), all deemed unrelated to selpercatinib. Only 12 (2%) patients discontinued therapy for treatment-related adverse events, of which, increased ALT (2) and drug hypersensitivity (2) were the most common. Abbreviations: ECG, electrocardiogram; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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CONCLUSIONS

- **Selpercatinib demonstrated robust and durable anti-tumor activity in *RET*-mutant MTC and *RET* fusion+ thyroid cancer**
  - Prior vandetanib and/or cabozantinib MTC (n=55):
    - Heavily pre-treated population (53% with ≥2 MKIs)
    - ORR 69% (95% CI: 55–81)
    - Median DoR not reached (95% CI: 19–NE), median PFS not reached (95% CI: 24–NE)
    - Significant and stable reductions in calcitonin and CEA in most patients.
  - Vandetanib/cabozantinib-naïve MTC (n=88): ORR 73% (95% CI 62–82), median DoR and PFS remain unstable with the majority of patients censored
  - Previously-treated *RET* fusion+ thyroid cancer (n=19): ORR 79% (95% CI: 54–94), median DoR was 18 months (95% CI: 7.6-NE), PFS was not reached (95% CI: 10-NE)
- **Favorable safety profile**
  - Safety database (n=531):
    - Most adverse events were low grade and unrelated to selpercatinib
    - Only 12 (2%) patients discontinued therapy for treatment-related adverse events
- **Outcomes with selpercatinib after treatment with approved MKIs were comparable to outcomes with MKIs when used in first line, and less toxic.**
- **Selpercatinib recently received approval for the treatment of *RET*-mutant MTC and *RET* fusion+ thyroid cancers** based on the results of the LIBRETTO-001 Phase 1/2 trial.
- **A randomized, global, phase 3 trial (LIBRETTO-531; NCT04211337)** of selpercatinib vs. cabozantinib or vandetanib (investigator's choice) in kinase inhibitor-naïve *RET*-mutant MTC was opened in Dec-2019.

Scan for full poster and/or slide deck

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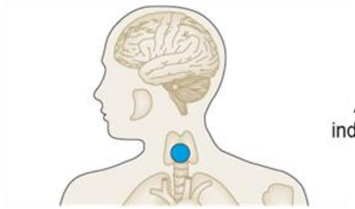
Background

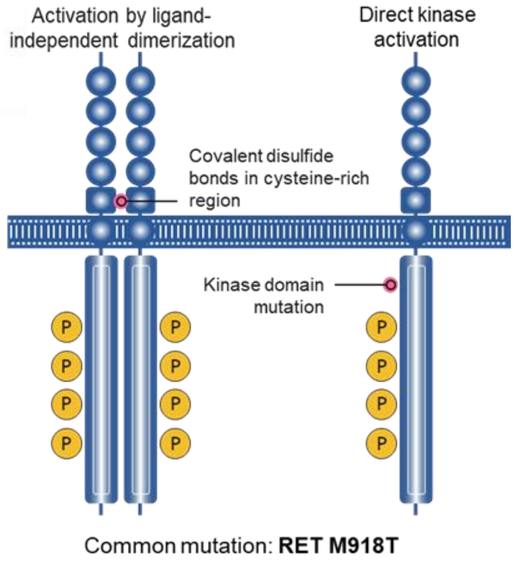
RET is activated by two major mechanisms in thyroid cancer

***RET* mutations**



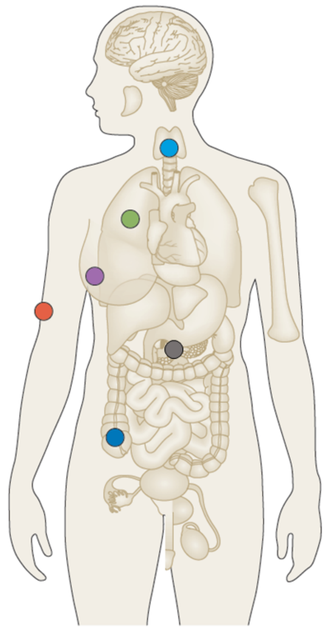
Medullary thyroid cancer

sporadic (>60%)
hereditary (>90%)

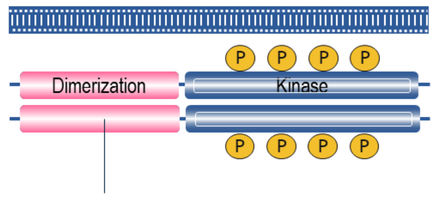


Common mutation: **RET M918T**

***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%)



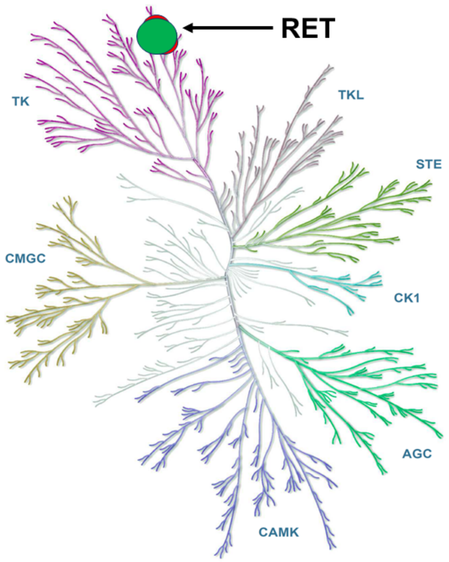
KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

- Anti-RET multikinase inhibitors (MKIs) are approved for medullary thyroid cancer and differentiated thyroid cancers but are highly toxic.
- The efficacy of these MKIs is ultimately limited by incomplete inhibition of RET in tumors in patients, significant toxicity from stronger inhibition of other targets (e.g., KDR/VEGFR2, EGFR, MET), and poor pharmacokinetics (i.e., significant drug accumulation and long half-life contributing to toxicity but not efficacy) in patients.

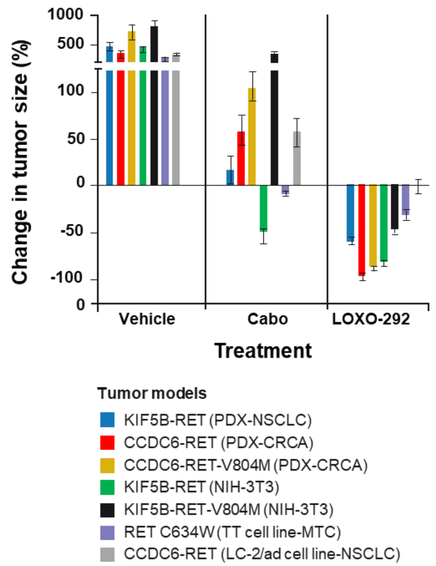
Drilon et al. Nat Rev Clin Oncol. 2018; 15:151–67; Kato et al. Clin Cancer Res. 2017; 23:1988–97; Pietrantonio et al. Ann Oncol. 2018; 29:1394–401; Su et al. PLoS One. 2016; 11:e0165596.

Background (continued)

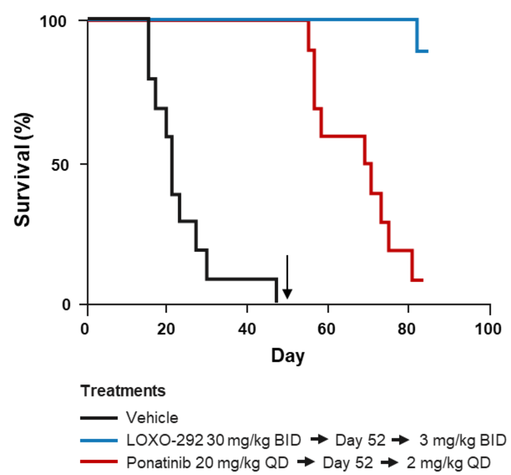
Kinome selectivity
Highly selective for RET



Xenograft models
Multiple fusions/mutations/histologies



Orthotopic brain model
CCDC6-RET orthotopic brain PDX



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- In an ongoing, first in human, phase 1/2 trial, selpercatinib treatment in patients with *RET*-altered cancers demonstrated marked and durable investigator-assessed antitumor activity in patients with *RET*-mutant medullary thyroid cancer (MTC), with or without prior vandetanib and/or cabozantinib therapy, and in patients with *RET* fusion+ thyroid cancer, and a tolerable safety profile.[2]
- In May 2020, selpercatinib was approved by the US FDA under the Accelerated Approval program for the treatment of 3 types of *RET*-altered cancers:
  - *RET* fusion-positive NSCLC
  - *RET*-mutant MTC
  - *RET* fusion-positive thyroid cancers

1. Subbiah V, et al. Ann Oncol. 2018;29:1869-1876. 2. Wirth L, et al. Ann Oncol. 2019;30(Supp 5):v933. Abbreviations: FDA, Food and Drug Administration; MTC, medullary thyroid cancer; NSCLC, non-small-cell lung cancer; US, United States.

OBJECTIVES

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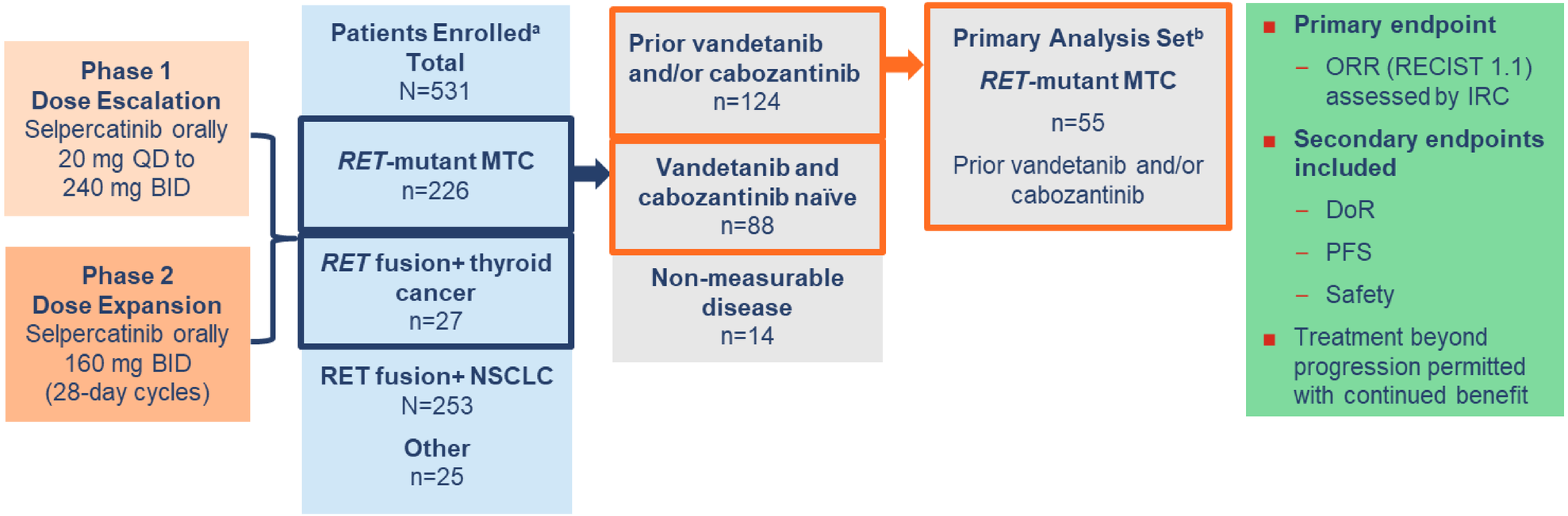
STUDY DESIGN



The Phase 1/2 LIBRETTO-001 Trial: Selpercatinib in Patients with *RET*-altered Cancers

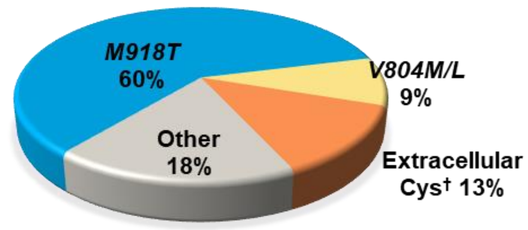
- An ongoing global, multicenter trial (NCT03157128) conducted in 16 countries and 89 sites.
- [a]Number of patients enrolled and treated as of 17-Jun-2019. Data cutoff date: 16-Dec-2019.
- [b]The primary analysis set (PAS) was defined through health authority agreement as the first 55 consecutively enrolled patients with *RET*-mutant MTC previously treated with vandetanib and/or cabozantinib. Patients with non-measurable disease enrolled in Phase 1 dose escalation were included in the PAS.
- *RET* alteration determined by local CLIA or similarly accredited laboratories using next-generation sequencing, FISH, or PCR.
- **Key inclusion criteria**: Age of ≥18 years or ≥12 years if permitted by regulatory authorities, diagnosis of advanced or metastatic solid tumor, ECOG PS 0 to 2, QTc of ≤470 msec, and adequate organ function.

Abbreviations: BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IRC, independent review committee; MTC, medullary thyroid cancer; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PCR, polymerase chain reaction; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

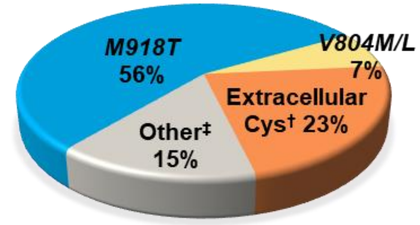
Baseline Patient Characteristics

Characteristic n (%) unless otherwise stated	*RET*-mutant MTC Vande and/or Cabo Pretreated (n=55)	*RET*-mutant MTC Vande/Cabo Naïve (n=88)	*RET* Fusion+ Thyroid Cancer (n=19)
Age, Median (range), year	57 (17–84)	58 (15–82)	54 (25–88)
Sex			
Male	36 (66)	58 (66)	9 (47)
Female	19 (35)	30 (34)	10 (53)
Race*			
White	49 (89)	75 (85)	14 (74)
Asian	0	4 (5)	2 (11)
Black or African American	1 (2)	1 (1)	1 (5)
Other	5 (9)	8 (9)	2 (11)
ECOG performance status			
0	11 (20)	43 (49)	5 (26)
1	41 (75)	42 (48)	12 (63)
2	3 (6)	3 (3)	2 (11)
Thyroid cancer tumor type			
Medullary	55 (100)	88 (100)	–
Papillary	–	–	13 (68)
Poorly differentiated	–	–	3 (16)
Hürthle cell	–	–	1 (5)
Anaplastic	–	–	2 (11)
Prior systemic regimens, median (range)	2 (1–8)	0 (0–2)	4 (1–7)
Prior vandetanib and/or cabozantinib**	55 (100)	–	–
Vandetanib only	18 (33)	–	–
Cabozantinib only	13 (24)	–	–
Vandetanib and cabozantinib	24 (44)	–	–
Prior radioactive iodine (RAI)**	–	–	16 (84)
Prior sorafenib and/or lenvatinib**	–	–	13 (68)
Prior multikinase inhibitor (MKI) therapy	55 (100)	7 (8)	15 (79)
1	26 (47)	6 (7)	7 (37)
≥2	29 (53)	1 (1)	8 (42)
Prior non-MKI therapy	17 (31)	9 (10)	14 (74)
Brain metastases	4 (7)	2 (2)	6 (32)

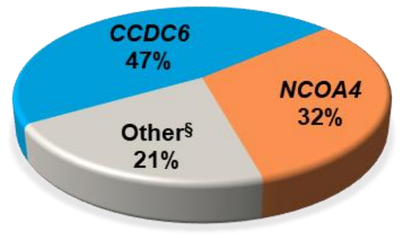
***RET* Alterations**



Vandetanib and/or cabozantinib pretreated MTC (n=55)



Vandetanib and cabozantinib naïve MTC (n=88)

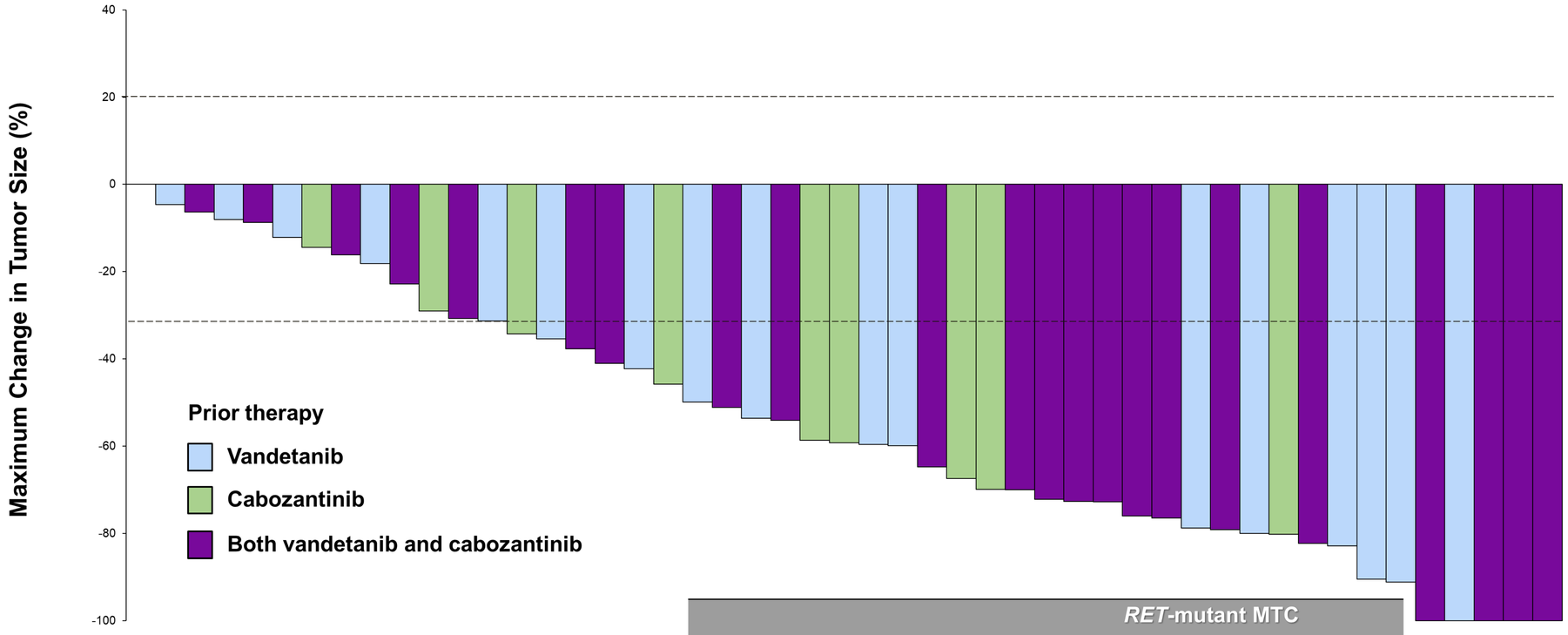


***RET* fusion+ thyroid cancer (n=19)**

*Includes 1 *RET* fusion-positive patient with missing race. **Prior cancer treatments relevant to disease type are presented. †Extracellular cysteine mutation defined as mutation including at least 1 of the following cysteine residues: 609, 611, 618, 620, 630, and 634. ‡Other includes: D631-L633delinsE, E632-L633del, A883F, D631-L633delinsV, L790F, D898-E901del, D898_E901del + D903_S904delinsEP, K666N, T636-V637insCRT, D378-G385delinsE. §Fusions identified in single tumors included *CCDC186-RET*, *ERC1-RET*, *KTN1-RET*, and *RUFY3-RET*. Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating greater disability. Total % may be different than the sum of the individual components due to rounding. Abbreviations, Cabo, cabozantinib; Vande, vandetanib.

KEY RESULTS

Marked Antitumor Activity with Selpercatinib in Patients with *RET*-mutant MTC Pretreated with Vandetanib and/or Cabozantinib, as Assessed by Independent Review Committee

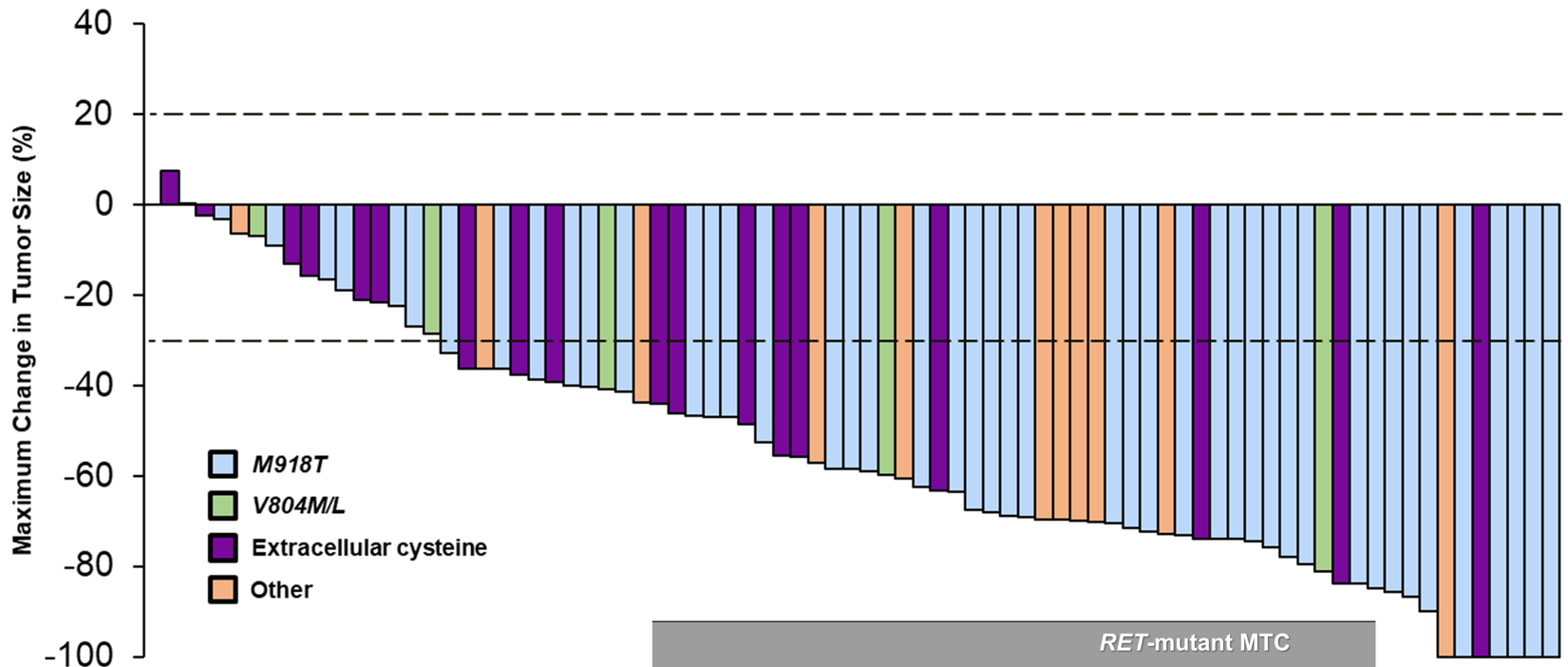


Data cutoff: 16-Dec-2019. For each patient, the maximum change in tumor size, defined as the best % change from baseline in the sum of diameters for all target lesions, is represented by a vertical bar in the waterfall plot. 7 patients are not shown as 2 discontinued prior to post-baseline imaging assessments, and 5 had non-measurable disease at baseline. Abbreviation: IRC, independent review committee; ORR, objective response rate.

	RET-mutant MTC Vandetanib and/or Cabozantinib Pretreated (n=55)
ORR by IRC, % (95% CI)	**69 (55–81)**
Best response by IRC, n (%)	
Complete response (CR)	5 (9)
Partial response (PR)	33 (60)
Stable disease (SD)	14 (26)
Progressive disease (PD)	1 (2)
Not evaluable (NE)	2 (4)

KEY RESULTS (continued)

Marked Antitumor Activity with Selpercatinib in Patients with *RET*-mutant MTC Naïve to Vandetanib/ Cabozantinib, as Assessed by Independent Review Committee

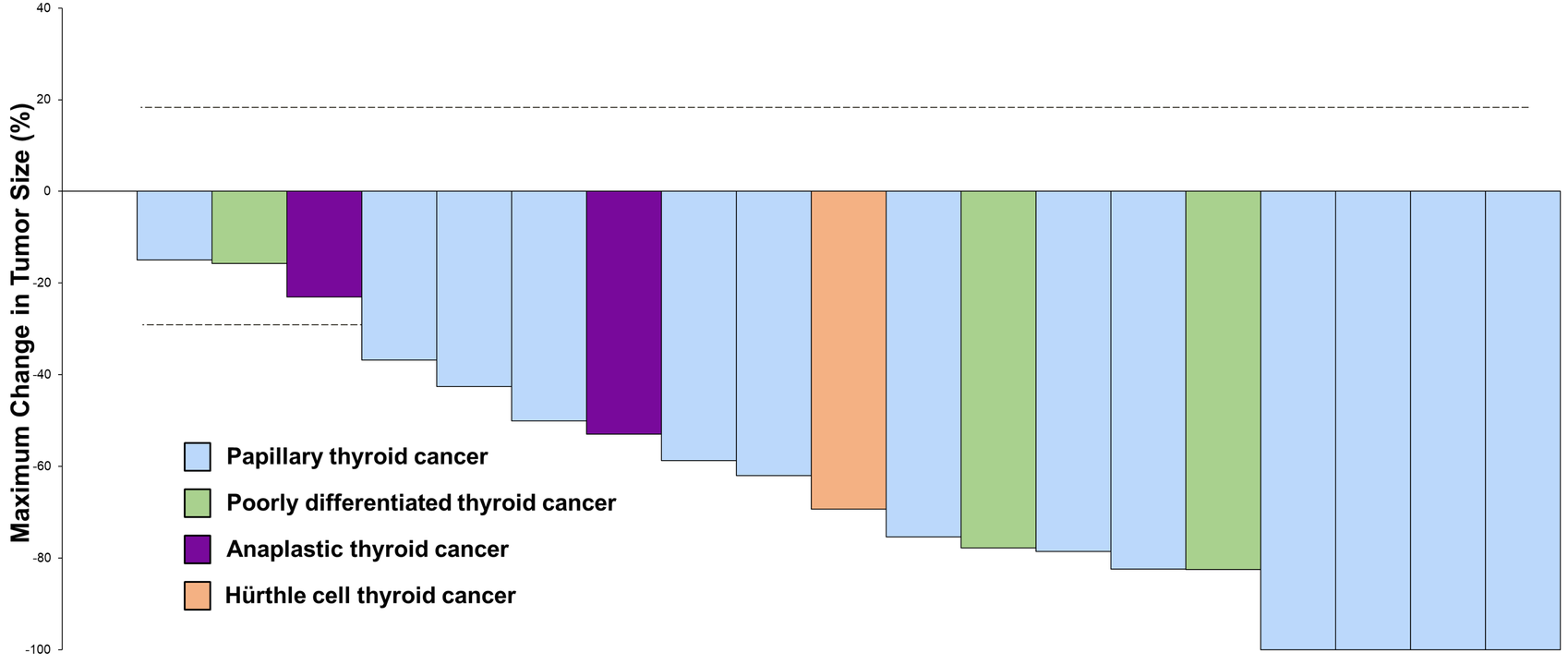


Data cutoff: 16-Dec-2019. For each patient, the maximum change in tumor size, defined as the best % change from baseline in the sum of diameters for all target lesions, is represented by a vertical bar in waterfall plot. 8 patients are not shown as 2 discontinued prior to post-baseline imaging assessments, and 6 had non-measurable disease at baseline. Abbreviations: IRC, independent review committee; ORR, objective response rate.

	RET-mutant MTC Vandetanib and Cabozantinib Naïve (n=88)
ORR by IRC, % (95% CI)	**73 (62–82)**
Best response by IRC, n (%)	
Complete response (CR)	10 (11)
Partial response (PR)	54 (61)
Stable disease (SD)	20 (23)
Progressive disease (PD)	2 (2)
Not evaluable (NE)	2 (2)

KEY RESULTS (continued)

Marked Antitumor Activity with Selpercatinib in Patients with Previously-Treated* *RET* Fusion+ Thyroid Cancer, as Assessed by Independent Review Committee

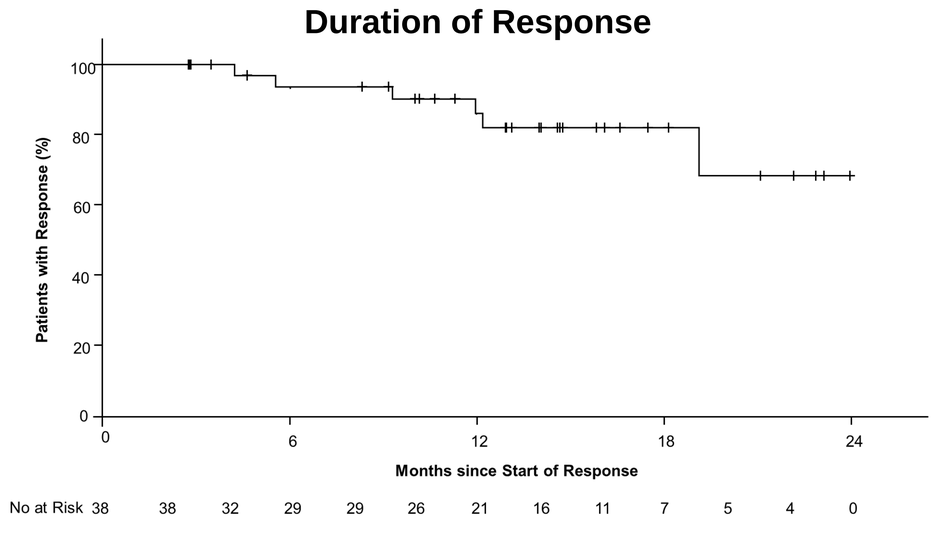


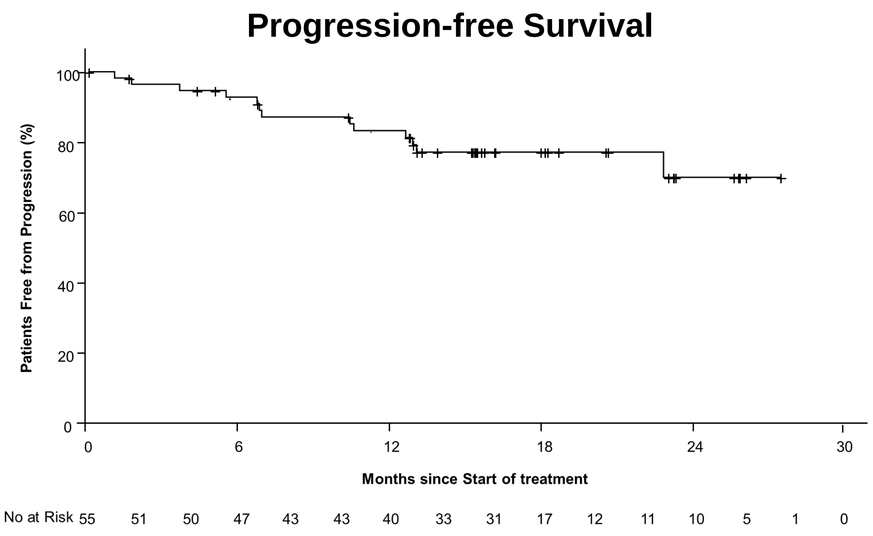
Data cutoff: 16-Dec-2019. *Prior systemic regimens, median (range): 4 (1–7). For each patient, the maximum change in tumor size, defined as the best % change from baseline in the sum of diameters for all target lesions, is represented by a vertical bar in waterfall plot. Abbreviations: IRC, independent review committee; ORR, objective response rate.

Previously-Treated* *RET* Fusion+ Thyroid Cancer (n=19)	
ORR by IRC, % (95% CI)	**79 (54–94)**
Best response by IRC, n (%)	
Complete response (CR)	1 (5)
Partial response (PR)	14 (74)
Stable disease (SD)	4 (21)
Progressive disease (PD)	0
Not evaluable (NE)	0

Durability of Efficacy in Prior Vandetanib and/or Cabozantinib-treated Patients

Selpercatinib Benefit in Prior Vandetanib and/or Cabozantinib-treated Patients with *RET*-mutant MTC, as Assessed by Independent Review Committee





- Median DoR was not reached (95% CI: 19 months–NE) with 32 of 38 (84%) responders censored with a median follow-up of 14 months.
- Median PFS was not reached (95% CI: 24 months–NE) with 42 of 55 (76%) patients censored with a median follow-up of 17 months.

Data cutoff: 16-Dec-2019. Abbreviations: DoR, duration of response; PFS, progression-free survival. NE, not estimable.

Durability of Efficacy in all Thyroid Cancer Treatment Groups

Selpercatinib Benefit in all Thyroid Cancer Treatment Groups as Assessed by Independent Review Committee and by Investigators

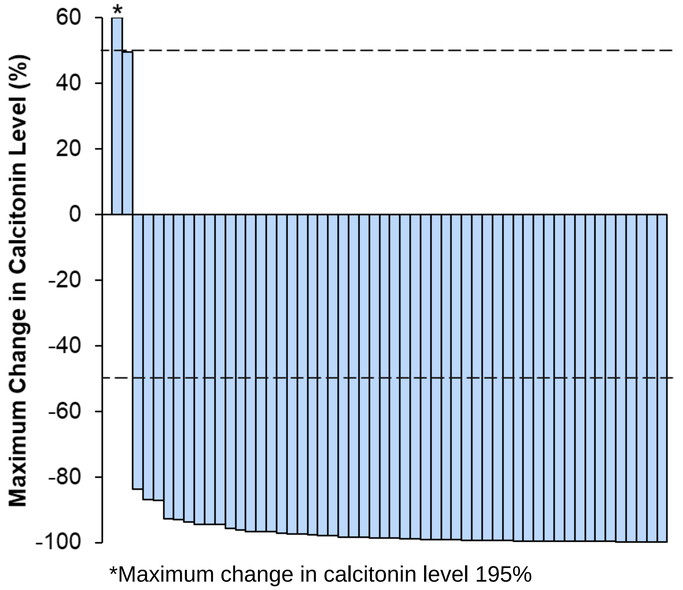
	RET-mutant MTC				Previously-Treated *RET* Fusion+ Thyroid Cancer	
	Vandetanib and/or Cabozantinib Pretreated		Vandetanib and Cabozantinib Naïve			
	Independent Review (n=55)	Investigator Assessment (n=55)	Independent Review (n=88)	Investigator Assessment (n=88)	Independent Review (n=19)	Investigator 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)	20 (9–NE)	NE (10–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 (37–82)	61 (33–81)

*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.

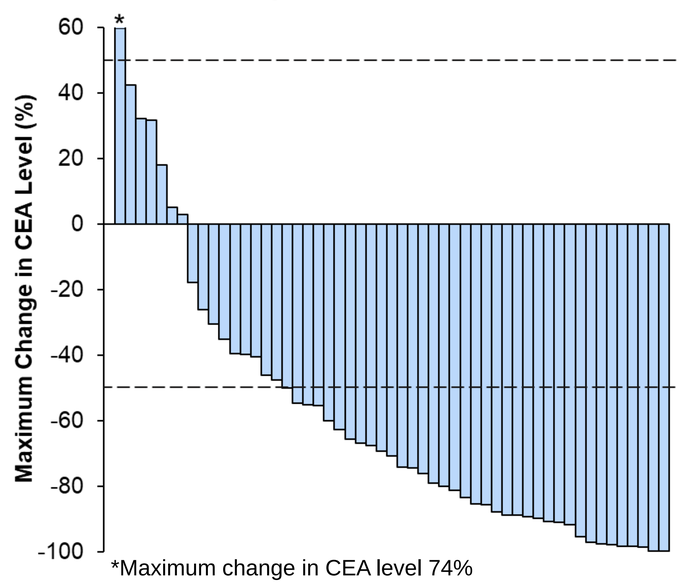
Biochemical Response in Patients with *RET*-mutant MTC Pretreated with Vandetanib and/or Cabozantinib

	RET-mutant MTC Vandetanib and/or Cabozantinib Pretreated	
	Calcitonin (n=54)	CEA (n=53)
ORR, % (95% CI)	**91 (80–97)**	**66 (52–79)**
Best response, n (%)		
Complete response (CR)	14 (26)	8 (15)
Partial response (PR)	35 (65)	27 (51)
Stable disease (SD)	0	9 (17)
Progressive disease (PD)	1 (2)	7 (13)
Not evaluable (NE)	4 (7)	2 (4)

Data cutoff: 16-Dec-2019. For patients with *RET*-mutant MTC pretreated with vandetanib and/or cabozantinib, serum calcitonin and carcinoembryonic antigen (CEA) levels were followed longitudinally. Best biochemical response for serum calcitonin and CEA was defined as follows: complete response, normalization of serum levels; partial response, ≥ 50% decrease from baseline levels; stable disease, if <50% decrease or increase from baseline; and progression if ≥50% increase from baseline (each maintained for at least 4 weeks).[1]



*Maximum change in calcitonin level 195%



*Maximum change in CEA level 74%

1. Wells SA, Jr. et al. Journal of Clinical Oncology. 2012;30:134-41.

Adverse Events with Selpercatinib

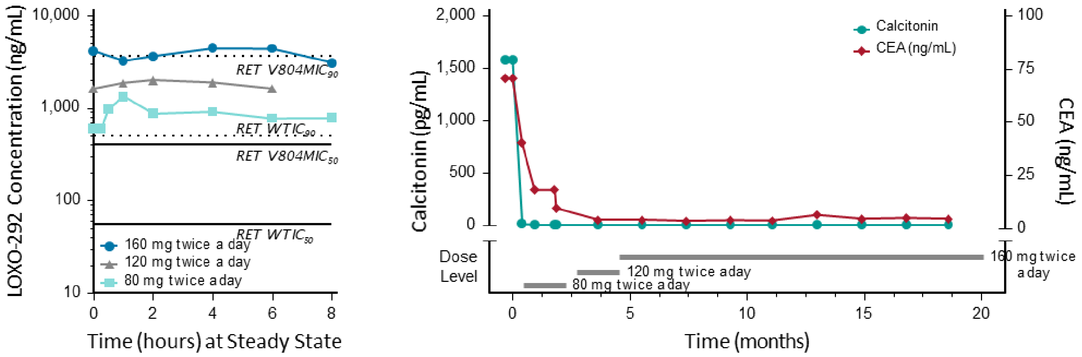
Adverse Events that Occurred at any Grade Regardless of Attribution in ≥15% of all Selpercatinib-treated Patients (N=531)

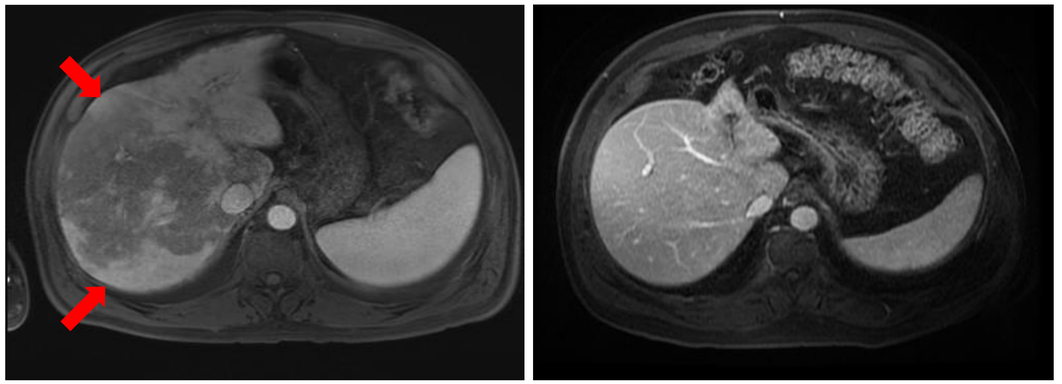
	Adverse Event, Regardless of Attribution					Treatment-related Adverse Event		
Adverse Event, %	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**
Diarrhea	27	9	4	–	40	2	–	22
Dry mouth	33	5	–	–	38	–	–	33
Hypertension	4	14	17	<1	36	11	<1	24
Aspartate aminotransferase increased	19	6	7	1	32	5	1	26
Fatigue	18	11	1	–	30	<1	–	18
Alanine aminotransferase increased	15	5	9	1	30	7	1	25
Nausea	21	6	1	–	27	<1	–	11
Constipation	21	5	1	–	27	<1	–	12
Edema peripheral	22	4	<1	–	27	–	–	15
Headache	18	5	2	–	24	<1	–	8
Blood creatinine increased	15	5	–	<1	21	–	–	11
Abdominal pain	14	5	2	–	20	<1	–	5
Rash	15	3	1	–	19	1	–	12
Vomiting	14	4	<1	–	18	<1	–	5
Cough	14	2	–	–	16	–	–	1
Electrocardiogram QT prolonged	5	7	4	–	16	3	–	12
Dyspnea	10	3	2	<1	16	–	–	1

Data cutoff: 16-Dec-2019. The relatedness of adverse events (AEs) to treatment was determined by the investigators. Total % for any given AE may be different than the sum of the individual grades, due to rounding. In total, 19 patients experienced grade 5 AEs including cardiac arrest (3), sepsis (3), respiratory failure (2), brain herniation, cardiac failure, cerebral hemorrhage, cerebrovascular accident, general physical health deterioration, hemoptysis, hypoxia, multiple organ dysfunction syndrome, neoplasm progression, pneumonia, and post-procedure hemorrhage (one each), all deemed unrelated to selpercatinib. Only 12 (2%) patients discontinued therapy for treatment-related adverse events, of which, increased alanine aminotransferase (2) and drug hypersensitivity (2) were the most common.

Selpercatinib Overcomes Germline *RET V804M* Gatekeeper Mutation

- 56-year-old man with hereditary *RET* V804M-mutant MTC
- Massive metastatic infiltration of the liver
- 3 prior anti-*RET* MKIs: cabozantinib, vandetanib, lenvatinib
- Initiated selpercatinib at 80 mg BID with escalation to 160 mg BID
- Rapid reduction in serum CEA and calcitonin, resolution of diarrhea, abdominal distension, and abdominal pain
- Confirmed CR by RECIST 1.1 after 8 weeks of treatment
- Remains on treatment at 25 months





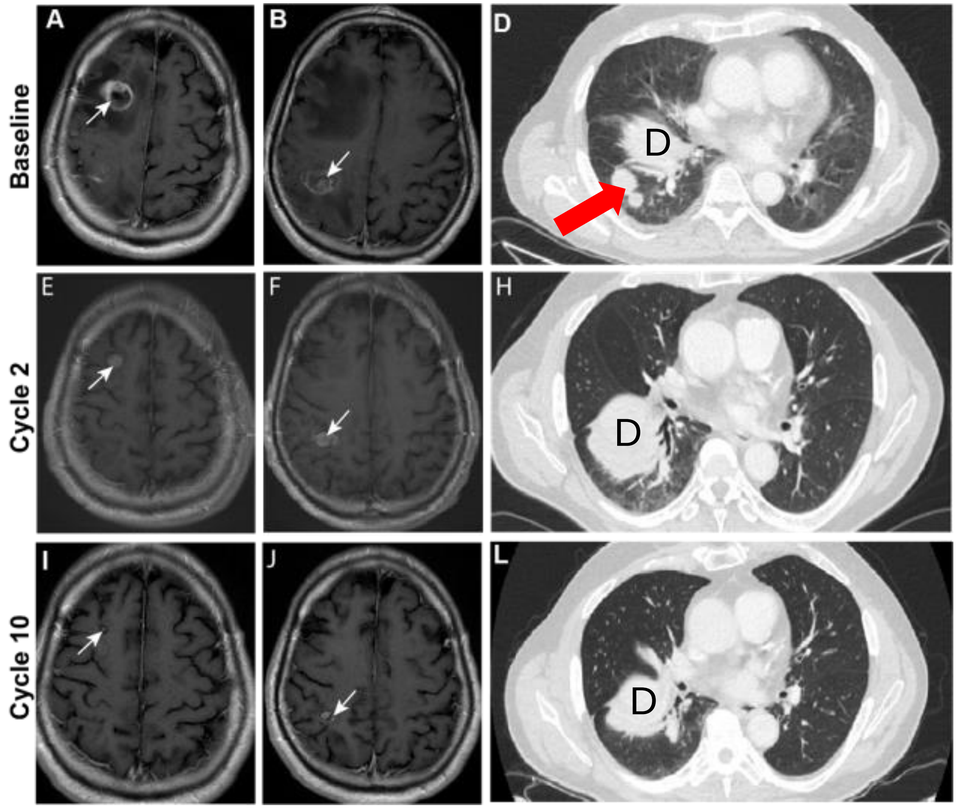
Baseline **Cycle 2**

Data cutoff: 16-Dec-2019. Red arrows indicate target lesions. Copyright for image and graphs owned by American Society of Clinical Oncology © 2019.

Wirth L, et al. JCO Precision Oncology. 2019; doi: 10.1200/PO.19.00189

Selpercatinib Activity in *CCDC6-RET* Fusion+ Anaplastic Thyroid Cancer

- 73-year-old man with *CCDC6-RET* fusion+ anaplastic thyroid cancer
- Metastatic disease to lungs and brain*
- Previous surgery, SRS, and docetaxel/doxorubicin
- Initiated selpercatinib at 160 mg BID
- Confirmed PR by RECIST 1.1 after 8 weeks of treatment
- Remains on treatment at 19 months



Data cutoff: 16-Dec-2019. *All CNS lesions considered non-target due to prior radiation. Red arrow indicates target lesions, D – diaphragm.

Dias-Santagata D, et al. Thyroid. 2020; ahead of print doi 10.1089/thy.2019.0477

CONCLUSIONS

- **Selpercatinib demonstrated robust and durable anti-tumor activity in *RET*-mutant MTC and *RET* fusion+ thyroid cancer**
  - Prior vandetanib and/or cabozantinib MTC (n=55):
    - Heavily pre-treated population (53% with ≥2 MKIs)
    - ORR 69% (95% CI: 55–81)
    - Median DoR not reached (95% CI: 19–NE), median PFS not reached (95% CI: 24–NE)
    - Significant and stable reductions in calcitonin and CEA in most patients.
  - Vandetanib/cabozantinib-naïve MTC (n=88): ORR 73% (95% CI 62–82), median DoR and PFS remain unstable with the majority of patients censored
  - Previously-treated *RET* fusion+ thyroid cancer (n=19): ORR 79% (95% CI: 54–94), median DoR was 18 months (95% CI: 7.6-NE), PFS was not reached (95% CI: 10-NE)
- **Favorable safety profile**
  - Safety database (n=531):
    - Most adverse events were low grade and unrelated to selpercatinib
    - Only 12 (2%) patients discontinued therapy for treatment-related adverse events

- **Outcomes with selpercatinib after treatment with approved MKIs were comparable to outcomes with MKIs when used in first line, and less toxic.**
- **Selpercatinib recently received approval for the treatment of *RET*-mutant MTC and *RET* fusion+ thyroid cancers** based on the results of the LIBRETTO-001 Phase 1/2 trial.
- **A randomized, global, phase 3 trial (LIBRETTO-531; NCT04211337)** of selpercatinib vs. cabozantinib or vandetanib (investigator's choice) in kinase inhibitor-naïve *RET*-mutant MTC was opened in Dec-2019.