Durability of Response With Selpercatinib in Patients With *RET*-Activated Thyroid Cancer: Long-Term Safety and Efficacy From LIBRETTO-001

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

LIBRETTO-001 is a registrational phase I/II, single-arm, open-label study of selpercatinib in patients with *RET* (REarranged during Transfection)-activated cancers (ClinicalTrials.gov identifier: NCT03157128). We present long-term safety and efficacy from LIBRETTO-001 in patients with *RET*-mutant medullary thyroid cancer (MTC; n = 324) and *RET* fusion-positive thyroid cancer encompassing different histological subtypes (TC; n = 66). At the data cutoff of January 2023, the objective response rate was 82.5% among patients with cabozantinib/vandetanib-naïve MTC and 95.8% among patients with treatment-naïve TC. At a median follow-up time of 42.4 and 44.0 months in patients with cabozantinib/vandetanib-naïve and pretreated MTC, the median progression-free survival (PFS) was not reached and 41.4 months, respectively. At a median follow-up time of 24.9 and 30.4 months in patients with treatment-naïve and pretreated TC, the median PFS was not reached and 27.4 months, respectively. Three-year PFS rates were 75.2% and 87.3% among patients with cabozantinib/vandetanib-naïve MTC and treatment-naïve TC, respectively. Median PFS was similar to median duration of response for each patient group. The safety profile of selpercatinib was consistent with previous reports. With an additional follow-up of 37 months and 228 more patients from the last disclosure, selpercatinib continued to provide durable and robust responses in treatment-naïve and previously treated patients with *RET*-mutant MTC and *RET* fusion-positive TC.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Selpercatinib, a first-in-class, highly selective, and potent *RET* (REarranged during Transfection) inhibitor, is currently approved in several regions around the world, including the United States, European Union, and Japan, for treatment of *RET*-mutant medullary thyroid cancer (MTC) and *RET* fusion-positive thyroid cancer (TC) encompassing different histological subtypes in adults and adolescents (age ≥12 years).[1-3] These initial approvals were based on the clinical benefits reported in the LIBRETTO-001 trial (ClinicalTrials.gov identifier: NCT03157128) in which selpercatinib demonstrated high response rates and favorable toxicity in both treatment-naïve and previously treated patients.[4] With over 3 years of additional follow-up and more than twice as many patients, we present the long-term results from safety and efficacy analyses of selpercatinib in patients with *RET*-activated MTC and TC from the LIBRETTO-001 clinical trial.

METHODS

Study Design

In the previously published phase I/II, open-label LIBRETTO-001 trial,[4,5] patients received oral selpercatinib (capsule or liquid), in 28-day continuous cycles at doses of 20 mg once daily to 240 mg twice daily during the dose-escalation phase. The recommended 160 mg twice daily dose was used in phase II.[4,5] Treatment continued until progressive disease, death, withdrawal of consent, or unacceptable toxicity. Patient enrollment required the identification of a prospective *RET* alteration (fusion or mutation). A positive germline DNA test for a *RET* mutation was acceptable for patients with MTC. Patients with *RET*-mutant MTC who were cabozantinib/vandetanib naïve were also required to have radiographic progressive disease within the previous 14 months. Before enrollment, the

sponsor reviewed and confirmed the results of local molecular testing conducted in a certified laboratory using next-generation sequencing, fluorescence in situ hybridization, or polymerase chain reaction to determine *RET* alteration status. This central confirmation of the locally identified *RET* alteration was not required. This report includes patients with *RET*-mutant MTC and *RET* fusion-positive TC of any histologic type who were treatment-naïve or treated with prior systemic therapy. Prior exposure to a *RET* inhibitor was an exclusion criterion except for patients in cohort 6 (MTC: n = 8; TC: n = 1), who were excluded from the efficacy analyses but included in the safety analyses.

Efficacy and Safety Measures

Efficacy and safety assessments were performed in patients enrolled in the LIBRETTO-001 study as previously described.[4,5] The primary end point was objective response rate (ORR). Responses were determined by an independent review committee of expert radiologists according to RECIST, version 1.1. Secondary end points included clinical benefit rate, progression-free survival (PFS), duration of response (DoR), and overall survival (OS). All responses necessitated validation through a subsequent consecutive scan obtained no less than 4 weeks after the initial scan indicating a response. Patients who were alive or lost to follow-up as of the data analysis cutoff date were censored. Safety was analyzed through adverse event (AE) reporting, graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Methods

The data cutoff date for this analysis was January 13, 2023. Confidence intervals (CIs) for response rates were calculated using the Clopper-Pearson method. DoR, PFS, and OS were estimated using the Kaplan-Meier method. The CI for the median survival time was derived following the method outlined by Brookmeyer and Crowley.[6] The reverse Kaplan-Meier method was used to estimate median follow-up times. Median follow-up durations were provided for each efficacy end point to provide additional context. Additional statistical analysis methodology is reported in the Protocol (online only).

RESULTS

Patient Demographics and Follow-Up

Among the 837 patients enrolled from May 2017 to May 2022, 324 had *RET*-mutant MTC and 66 had *RET* fusion-positive TC. The baseline characteristics and demographics are presented in Table 1 and Data Supplement (Table S1, online only). Prior systemic therapy use is shown in the Data Supplement (Table S2). The median follow-up duration and range for each subgroup and each efficacy end point are presented in the Data Supplement (Table S3).

RET-Mutant MTC

Three groups of patients with *RET*-mutant MTC were analyzed: (1) treatment-naïve patients (n = 116); (2) cabozantinib/vandetanib-naïve patients (may have received other systemic therapies; n = 143); and (3) patients previously treated with any multikinase inhibitor (MKI; n = 152). The treatment-naïve cohort (n = 116) was a subset of the cabozantinib/vandetanib-naïve cohort (n = 143); response outcomes were reported for patients in the cabozantinib/vandetanib-naïve cohort as outcomes were not meaningfully different between these two cohorts. Response outcomes are presented in Table 2, Figure 1, and the Data Supplement (Table S4 and Figs S1-S5).

The ORR was 84.5% (95% CI, 76.6 to 90.5) in treatment-naïve patients and 82.5% (95% CI, 75.3 to 88.4) in cabozantinib/vandetanib-naïve patients, with 25.9% and 23.8%, respectively, achieving a complete response (CR). The ORR was 77.6% (95% CI, 70.2 to 84.0) in patients previously treated with MKIs, with 12.5% of patients achieving a CR. In the overall MTC cohort (N = 295), ORR was 79.5% (95% CI, 72.9 to 85.0) in patients with an *M918T RET* mutation and 80.9% (95% CI, 72.3 to 87.8) in patients with other mutation types.

The median DoR was not reached (95% CI, 51.3 to not evaluable [NE]) in the cabozantinib/vandetanib-naïve group (median follow-up, 39.4 months). The median DoR in patients previously treated with MKIs (median follow-up, 38.3 months) was 45.3 months (95% CI, 33.6 to NE). At 4 years, 67.6% (95% CI, 55.6 to 77.0) of the cabozantinib/vandetanib-naïve group had responses that were ongoing. In the overall cohort, DoR was not reached in patients with an *M918T RET* mutation (95% CI, 51.3 to NE) or other mutation types (95% CI, 36.8 to NE).

At a median follow-up of 42.4 months, the median PFS was not reached (95% CI, 53.1 to NE) in the cabozantinib/vandetanib-naïve group. In patients previously treated with MKIs and with a follow-up of 44.0 months, the median PFS was 41.4 months (95% CI, 30.2 to NE). Three-year PFS rates were 75.2% (95% CI, 66.8 to 81.8) and 54.6% (95% CI, 45.6 to 62.8) in cabozantinib/vandetanib-naïve patients and patients previously treated with MKIs, respectively.

The median OS was not reached in the cabozantinib/vandetanib-naïve group (median follow-up, 44.6 months). In patients previously treated with MKIs with a median follow-up of 46.9 months, the median OS was 64.3 months. Three-year OS rates were 89.7% among cabozantinib/vandetanib-naïve patients and 67.8% among patients previously treated with MKIs.

RET Fusion-Positive TC

Two groups of patients with *RET* fusion-positive TC were analyzed: (1) systemic treatment-naïve patients (other

TABLE 1. Clinicopathologic Features in RET Fusion-Positive TC and RET-Mutant Medullary Thyroid Cancer (MTC)

	RET Fusion-Positive TC		*RET*-Mutant MTC	
Characteristic	Treatment Naïve (n = 24)[a]	Previously Treated (n = 41)	Cabozantinib/Vandetanib Naïve (n = 143)[b]	Previously Treated (n = 152)
Age, years, median (range)	60.5 (20-84)	58.0 (25-88)	57.0 (15-87)	58.0 (17-90)
Sex, No. (%)				
Female	10 (41.7)	23 (56.1)	60 (42.0)	55 (36.2)
Male	14 (58.3)	18 (43.9)	83 (58.0)	97 (63.8)
Race, No. (%)				
White	18 (75.0)	24 (58.5)	124 (86.7)	137 (90.1)
Asian	1 (4.2)	12 (29.3)	8 (5.6)	2 (1.3)
Black	0	3 (7.3)	2 (1.4)	2 (1.3)
Native Hawaiian or other Pacific Islander	0	0	1 (0.7)	0
American Indian or Alaska Native	0	0	0	1 (0.7)
Other	3 (12.5)	2 (4.9)	7 (4.9)	10 (6.6)
Missing	2 (8.3)	0	1 (0.7)	0
Smoking status, No. (%)				
Never	12 (50.0)	28 (68.3)	NR	NR
Former	10 (41.7)	13 (31.7)	NR	NR
Current	1 (4.2)	0	NR	NR
Missing	1 (4.2)	0	NR	NR
ECOG performance status, No. (%)				
0	14 (58.3)	11 (26.8)	69 (48.3)	42 (27.6)
1	9 (37.5)	27 (65.9)	68 (47.6)	99 (65.1)
2	1 (4.2)	3 (7.3)	6 (4.2)	11 (7.2)
TC histologic subtype, No. (%)				
Papillary TC	23 (95.8)	31 (75.6)	—	—
Poorly differentiated TC	1 (4.2)	5 (12.2)	—	—
Anaplastic TC	0	4 (9.8)	—	—
Hurthle cell TC	0	1 (2.4)	—	—
MTC	0	0	143 (100)	152 (100)
No. of prior systemic regimens, (%)				
0	6 (25.0)	0	116 (81.1)	—
1	10 (41.7)	10 (24.4)	22 (15.4)	73 (48.0)
2	3 (12.5)	8 (19.5)	5 (3.5)	37 (24.3)
≥3	5 (20.8)	23 (56.1)	0	42 (27.6)

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TABLE 1. Clinicopathologic Features in RET Fusion-Positive TC and RET-Mutant Medullary Thyroid Cancer (MTC) (continued)

	RET Fusion-Positive TC		*RET*-Mutant MTC	
Characteristic	Treatment Naïve (n = 24)[a]	Previously Treated (n = 41)	Cabozantinib/Vandetanib Naïve (n = 143)[b]	Previously Treated (n = 152)
Previous regimen,[c] No. (%)				
Chemotherapy	—	8 (19.5)	5 (3.5)	16 (10.5)
Immunotherapy	—	3 (7.3)	5 (3.5)	13 (8.6)
Multikinase inhibitor	—	35 (85.4)	9 (6.3)	152 (100)
Other[d]	18 (75.0)	30 (73.2)	9 (6.3)	16 (10.5)
RET fusion, No. (%)				
CCDC6	15 (62.5)	25 (61.0)	—	—
NCOA4	7 (29.2)	8 (19.5)	—	—
Other	2 (8.3)	7 (17.1)	—	—
Unknown	0	1 (2.4)	—	—
RET mutation type, No. (%)				
M918T	—	—	86 (60.1)	99 (65.1)
Extracellular cysteine mutation	—	—	34 (23.8)	24 (15.8)
V804 M/L	—	—	6 (4.2)	8 (5.3)
Other	—	—	17 (11.9)	21 (13.8)
CNS metastases at baseline,[e] No. (%)				
Yes	1 (4.2)	12 (29.3)	3 (2.1)	11 (7.2)
No	23 (95.8)	29 (70.7)	140 (97.9)	141 (92.8)
Patients who received at least one dose of 160 mg twice daily, No. (%)	23 (95.8)	40 (97.6)	141 (98.6)	144 (94.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MTC, medullary thyroid cancer; mTOR, mammalian target of rapamycin; NR, not reported; *RET*, REarranged during Transfection; TC, thyroid cancer; VEGF, vascular endothelial growth factor.

[a]Treatment naïve refers to therapies other than radioactive iodine.

[b]Cabozantinib/vandetanib naïve included treatment-naïve patients (n = 116) and patients who were not previously treated with cabozantinib/vandetanib (n = 27).

[c]Patients may have received more than one prior systemic therapy.

[d]Other prior systemic therapies included radioactive iodine, mTOR inhibitor, EGFR inhibitor, VEGF/VEGF receptor inhibitor, hormonal therapy, and selective *RET* inhibitor.

[e]Includes both measurable and nonmeasurable CNS metastases.

TABLE 2. Efficacy in *RET* Fusion-Positive TC and *RET*-Mutant MTC

	RET Fusion-Positive TC		*RET*-Mutant MTC	
Response	Treatment Naïve (n = 24)[a]	Previously Treated (n = 41)	Cabozantinib/Vandetanib Naïve (n = 143)[b]	Previously Treated (n = 152)
Objective response rate by IRC,[c] % (95% CI)	95.8 (78.9 to 99.9)	85.4 (70.8 to 94.4)	82.5 (75.3 to 88.4)	77.6 (70.2 to 84.0)
Best overall response				
CR, No. (%)	5 (20.8)	5 (12.2)	34 (23.8)	19 (12.5)
PR, No. (%)	18 (75.0)	30 (73.2)	84 (58.7)	99 (65.1)
SD, No. (%)	1 (4.2)	6 (14.6)	20 (14.0)	25 (16.4)
PD, No. (%)	0	0	2 (1.4)	2 (1.3)
Not evaluable	0	0	3 (2.1)	7 (4.6)
Clinical benefit rate,[d,e] % (95% CI)	100 (85.8 to 100)	100 (91.4 to 100)	94.4 (89.3 to 97.6)	91.4 (85.8 to 95.4)
DoR				
Median (95% CI)[f,g] months	NE (42.8 to NE)	26.7 (12.1 to NE)	NE (51.3 to NE)	45.3 (33.6 to NE)
Patients with censored data, No. (%)	21 (91.3)	20 (57.1)	87 (73.7)	72 (61.0)
Rate of DoR at median follow-up time, % (95% CI)	100 (100 to 100)	45.6 (25.6 to 63.6)	72.4 (62.2 to 80.3)	55.7 (44.8 to 65.3)
Rate of DoR,[g,h] % (95% CI)				
1 year	100 (NE to NE)	71.7 (52.4 to 84.2)	91.4 (84.6 to 95.3)	83.0 (74.6 to 88.8)
2 years	90.9 (50.8 to 98.7)	50.7 (30.4 to 67.8)	84.1 (75.9 to 89.7)	66.4 (56.3 to 74.7)
3 years	90.9 (50.8 to 98.7)	45.6 (25.6 to 63.6)	76.7 (67.4 to 83.7)	60.3 (49.8 to 69.3)
4 years	NE (NE to NE)	45.6 (25.6 to 63.6)	67.6 (55.6 to 77.0)	48.5 (36.2 to 59.7)
5 years	—	—	NE (NE to NE)	48.5 (36.2 to 59.7)
PFS				
Disease progression, No. (%)	3 (12.5)	16 (39.0)	33 (23.1)	53 (34.9)
Median (95% CI)[f,g] months	NE (44.2 to NE)	27.4 (14.5 to NE)	NE (53.1 to NE)	41.4 (30.2 to NE)
Patients with censored data, No. (%)	21 (87.5)	24 (58.5)	104 (72.7)	83 (54.6)
Rate of PFS at median follow-up time, % (95% CI)	87.3 (56.4 to 96.8)	49.5 (31.1 to 65.4)	70.2 (60.9 to 77.8)	47.8 (38.50 to 56.6)
Rate of PFS,[g,h] % (95% CI)				
1 year	95.2 (70.7 to 99.3)	70.6 (53.2 to 82.6)	91.1 (84.8 to 94.8)	79.5 (71.8 to 85.3)
2 years	95.2 (70.7 to 99.3)	57.1 (38.6 to 71.8)	82.5 (74.8 to 88.0)	64.9 (56.2 to 72.3)
3 years	87.3 (56.4 to 96.8)	49.5 (31.1 to 65.4)	75.2 (66.8 to 81.8)	54.6 (45.6 to 62.8)
4 years	65.5 (17.5 to 90.2)	49.5 (31.1 to 65.4)	65.9 (55.1 to 74.8)	45.9 (36.2 to 55.1)
5 years	NE (NE to NE)	49.5 (31.1 to 65.4)	NE (NE to NE)	41.6 (31.1 to 51.7)
OS				
Median (95% CI)[f,g] months	NE (NE to NE)	NE (25.3 to NE)	NE (NE to NE)	64.3 (48.3 to NE)
Patients with censored data, No. (%)	23 (95.8)	30 (73.2)	128 (89.5)	96 (63.2)
Rate of OS at median follow-up time, % (95% CI)	94.4 (66.6 to 99.2)	65.5 (46.0 to 79.4)	88.8 (82.0 to 93.1)	63.4 (54.7 to 70.9)

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TABLE 2. Efficacy in *RET* Fusion-Positive TC and *RET*-Mutant MTC (continued)

	RET Fusion-Positive TC		*RET*-Mutant MTC	
Response	Treatment Naïve (n = 24)[a]	Previously Treated (n = 41)	Cabozantinib/Vandetanib Naïve (n = 143)[b]	Previously Treated (n = 152)
Rate of OS,[g,h] % (95% CI)				
1 year	100 (NE to NE)	94.8 (80.7 to 98.7)	99.3 (95.0 to 99.9)	87.8 (81.3 to 92.1)
2 years	94.4 (66.6 to 99.2)	76.4 (58.1 to 87.5)	94.9 (89.7 to 97.5)	76.6 (68.8 to 82.7)
3 years	94.4 (66.6 to 99.2)	65.5 (46.0 to 79.4)	89.7 (83.3 to 93.8)	67.8 (59.4 to 74.8)
4 years	94.4 (66.6 to 99.2)	65.5 (46.0 to 79.4)	88.8 (82.0 to 93.1)	60.7 (51.5 to 68.7)
5 years	NE (NE to NE)	65.5 (46.0 to 79.4)	88.8 (82.0 to 93.1)	57.1 (47.1 to 65.9)

Abbreviations: CR, complete response; DoR, duration of response; IRC, independent review committee; MTC, medullary thyroid cancer; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; *RET*, REarranged during Transfection; SD, stable disease; TC, thyroid cancer.

[a]Treatment naïve refers to therapies other than radioactive iodine.

[b]Cabozantinib/vandetanib naïve included treatment-naïve patients (n = 116) and patients who were not previously treated with cabozantinib/vandetanib (n = 27).

[c]Objective response rate was defined as the proportion of patients with a best overall response of confirmed CR or PR.

[d]95% CI was calculated using the Clopper-Pearson method.

[e]Clinical benefit rate (%) was defined as the proportion of patients with a best overall response of a confirmed CR, PR, or SD lasting ≥16 weeks. SD was measured from the date of the first dose of selpercatinib until the criteria for PD were first met.

[f]95% CIs were calculated using the Brookmeyer-Crowley method.

[g]Estimate based on the Kaplan-Meier method.

[h]95% CIs were calculated using the Greenwood formula.

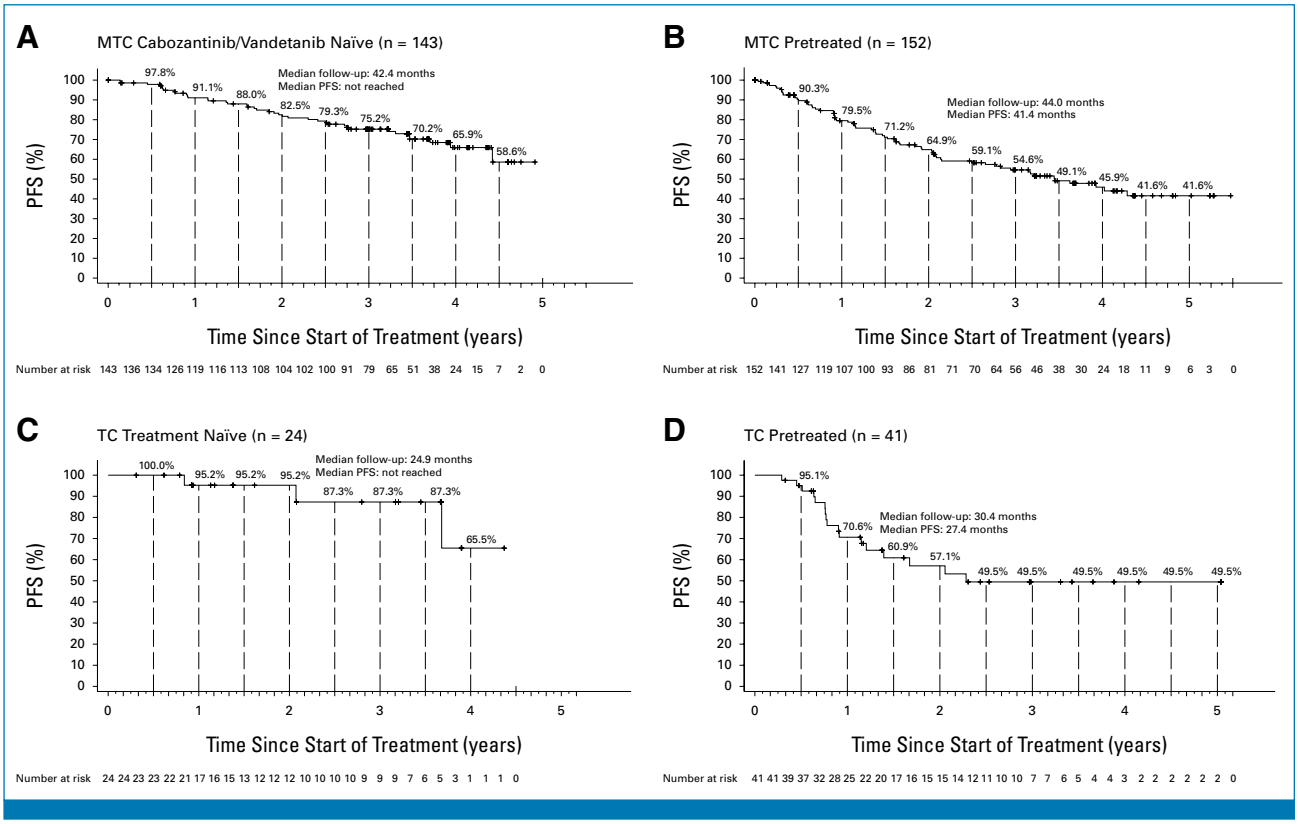

FIG 1. Long-term PFS with selpercatinib. Kaplan-Meier plots show PFS for the (A) *RET*-mutant MTC cabozantinib/vandetanib-naïve group, (B) *RET*-mutant MTC pretreated group, (C) *RET* fusion-positive TC treatment-naïve group, and (D) *RET* fusion-positive TC pretreated group. Tick marks indicate censored data. Eligible patients are defined as treated patients. Patients enrolled in phase II who discontinued selective *RET* inhibitor(s) because of intolerance were excluded. MTC, medullary thyroid cancer; PFS, progression-free survival; *RET*, REarranged during Transfection; TC, thyroid cancer.

than radioactive iodine therapy; n = 24) and (2) patients previously treated with any systemic therapy other than radioactive iodine (n = 41). Response outcomes are presented in Table 2, Figure 1, and the Data Supplement (Figs S1-S4).

The ORR was 95.8% (95% CI, 78.9 to 99.9) in treatment-naïve patients and 85.4% (95% CI, 70.8 to 94.4) in pretreated patients, with 20.8% and 12.2%, respectively, achieving a CR.

At a median follow-up of 17.8 months in the treatment-naïve group, the median DoR was not reached (95% CI, 42.8 to NE), and the 2-year response rate was 90.9%. In the pretreated group with a median follow-up of 33.9 months, the median DoR was 26.7 months (95% CI, 12.1 to NE), and the 4-year response rate was 45.6%.

The median PFS was not reached (95% CI, 44.2 to NE) in the treatment-naïve group at a median follow-up of 24.9 months and was 27.4 months (95% CI, 14.5 to NE; median follow-up, 30.4 months) in the pretreated group. Two-year PFS rates among patients in the treatment-naïve and pretreated groups were 95.2% and 57.1%, respectively.

At a median follow-up of 38.7 and 36.9 months, the median OS was not reached among treatment-naïve or pretreated groups, respectively. Three-year OS rates among patients in the treatment-naïve and pretreated groups were 94.4% and 65.5%, respectively.

Safety

Treatment-emergent AEs, serious AEs (SAEs) regardless of causality, and AEs deemed related to selpercatinib by the investigator are shown in the Data Supplement (Tables S5 and S6). The most common (≥5%) grade ≥3 treatment-emergent AEs were hypertension (MTC, 21.6%; TC, 15.2%) and increased ALT (MTC, 9.0%; TC, 6.1%). Grade ≥3 prolonged QT interval was observed in 4.3% and 4.5% of patients with MTC and TC, respectively. The most common grade ≥3 treatment-related AEs included hypertension (MTC, 14.5%; TC, 6.1%) and increased ALT (MTC, 7.4%; TC, 3.0%; Data Supplement, Table S5). The most common SAEs were pneumonia (4.6%) in patients with MTC and abdominal pain and confusional state (both 4.5%) in patients with TC (Data Supplement, Table S6). Ascites (1.5%) was the most common treatment-related SAE in patients with MTC. Abdominal pain, hyperbilirubinemia, vomiting, cholestasis,

and lymphopenia (one patient each) were the observed treatment-related SAEs in patients with TC.

DISCUSSION

Here, we report the long-term safety and efficacy data in patients with TC from the LIBRETTO-001 trial. Importantly, this disclosure builds on the initial publication for this patient population with a follow-up of over 3 years, demonstrating durability of response and describing long-term safety data with selpercatinib therapy.[4] Selpercatinib continued to demonstrate a potent response (with almost 70% of responses ongoing in cabozantinib/vandetanib-naïve patients at 4 years) and a consistent safety profile as previously described in this population of patients with *RET*-activated TC.

In the initial report from LIBRETTO-001 (N = 162; patients enrolled from May 2017 through June 2019), among cabozantinib/vandetanib-pretreated (n = 55) and treatment-naïve (n = 88) patients with *RET*-mutant MTC, ORRs were 69% and 73% with 1-year PFS rates of 82% and 92%, respectively.[4] In patients with *RET* fusion-positive TC (n = 19), the ORR was 79% and PFS at 1 year was 64%.[4] The current analysis demonstrates continued marked efficacy in a larger population of patients with MTC and TC. Moreover, selpercatinib demonstrates a favorable ORR, durable responses, and a tolerable safety profile both in patients with MTC and TC, without cumulative or late toxic effects.

MKIs, currently used as first-line treatment for MTC (cabozantinib and vandetanib) and papillary TC (lenvatinib and sorafenib), show modest efficacy and limited durability of responses. This is in part due to AEs, acquired resistance, and limited potency due to nonselectivity.[7-9] These data provide additional support to current guidelines[10] that recommend selpercatinib treatment for MTC and TC on identification of a *RET* alteration. Furthermore, we observed more favorable outcomes in patients with treatment-naïve *RET*-activated MTC and TC compared with previously treated patients. These data should be interpreted with caution since this analysis was not designed to compare outcomes between these groups of patients. However, recently disclosed data from the phase 3 LIBRETTO-531 trial showed superior PFS and treatment failure–free survival with first-line treatment with selpercatinib compared with cabozantinib or vandetanib in patients with *RET*-mutant MTC.[11] The AE profile reported here is also consistent with that reported in the LIBRETTO-531 trial, with notable AEs such as liver enzyme elevation, prolonged QT interval as documented on an ECG, and hypertension.[11] More importantly, the safety profile remains unchanged despite longer treatment with selpercatinib.

In conclusion, selpercatinib continued to demonstrate durable and potent efficacy with a consistent safety profile in a larger number of patients with *RET*-mutant MTC and *RET* fusion-positive TC, regardless of line of therapy, after longer follow-up. Testing for *RET* alterations in MTC and TC should be performed before initiating systemic therapy to identify patients who will benefit from *RET* inhibition with selpercatinib treatment.[12]

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DATA SHARING STATEMENT

Eli Lilly and Company provides access to all individual data collected during the trial, after anonymization, with the exception of pharmacokinetic, genomic, or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication

acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org. A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO.23.02503.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Durability of Response With Selpercatinib in Patients With *RET*-Activated Thyroid Cancer: Long-Term Safety and Efficacy From LIBRETTO-001

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