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ORIGINAL RESEARCH

Patient-reported outcomes with selpercatinib treatment in patients with *RET*-driven cancers in the phase I/II LIBRETTO-001 trial☆

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Background: This *post-hoc* retrospective study describes long-term patient-reported outcomes (PROs) for ***RE***arranged during ***T***ransfection (*RET*)-altered non-small-cell lung cancer (NSCLC), medullary thyroid cancer (MTC), non-MTC thyroid cancer (TC), and tumor agnostic (TA) patients (Data cut-off: January 2023) from the LIBRETTO-001 trial.

Patients and methods: Patients completed the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30). Patients with MTC also completed a modified version of the Systemic Therapy-Induced Diarrhea Assessment Tool (mSTIDAT). The proportion of patients with improved, stable, or worsened status after baseline was reported. PROs were summarized at 3 years (cycle 37) post-baseline for the NSCLC and MTC cohorts, and at 2 years (cycle 25) post-baseline for the TC and TA cohorts. Time-to-event outcomes (time to first improvement or worsening and duration of improvement) were reported.

Results: The baseline assessment was completed by 200 (63.3%), 209 (70.8%), 50 (76.9%), and 38 (73.1%) patients in the NSCLC, MTC, TC, and TA cohorts, respectively. The total compliance rate was 80%, 82%, 70%, and 85%, respectively. Approximately 75% (NSCLC), 81% (MTC), 75% (TC), and 40% (TA) of patients across all cohorts reported improved or stable QLQ-C30 scores at year 3 (NSCLC and MTC) or year 2 (TC and TA) with continuous selpercatinib use. Across cohorts, the median time to first improvement ranged from 2.0 to 19.4 months, the median duration of improvement ranged from 1.9 to 28.2 months, and the median time to first worsening ranged from 5.6 to 44.2 months. The total compliance rate for the mSTIDAT was 83.7% and the proportion of patients with MTC who reported diarrhea on the mSTIDAT was reduced from 80.8% at baseline to 35.6% at year 3.

Conclusions: A majority of patients with *RET*-driven cancers improved or remained stable on most QLQ-C30 domains, demonstrating favorable health-related quality of life as measured by the QLQ-C30 during long-term treatment with selpercatinib.

Key words: rearranged during transfection (*RET*), selpercatinib, patient-reported outcomes (PROs), health-related quality of life (HRQoL), non-small-cell lung cancer (NSCLC), medullary thyroid cancer (MTC), tumor agnostic (TA)

INTRODUCTION

Oncogenic alterations in ***RE***arranged during *T*ransfection (*RET*), a receptor tyrosine kinase, manifest in several cancers including non-small-cell lung cancer (NSCLC), medullary thyroid cancer (MTC), papillary thyroid cancer (TC), and tumor-agnostic non-lung, non-thyroid solid cancers (TA).[1] These alterations trigger *RET* kinase activation and promote tumorigenesis through point mutations in nearly all types of hereditary MTC and ∼50% of sporadic MTC. *RET* alterations drive tumor development through gene rearrangements that create *RET* fusions in 1%-2% of NSCLC and other cancers including colorectal and breast cancer.[1] The health-related quality of life (HRQoL) of patients with advanced/metastatic NSCLC is negatively impacted by symptoms such as fatigue, cough, difficulty breathing, and appetite loss.[2] Patients with MTC may experience diarrhea as an adverse effect of treatment with multikinase inhibitors (MKIs) such as vandetanib or cabozantinib, which can be debilitating and lead to workplace absence and lost productivity.[3-7] Patients with TC have decreased HRQoL compared with the general population, reporting adverse

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events associated with thyroid surgery and/or radioactive iodine treatment.[8-11]

A recent study reported that patients with MTC who received prior treatment with MKIs experienced an improvement in global health status (GHS)/quality of life (QoL) and functioning and a reduction in diarrhea after being treated with pralsetinib [a *RET* tyrosine kinase inhibitor (TKI)].[12] Another *RET* TKI, selpercatinib, which is a first-in-class, highly selective, and potent *RET* inhibitor, has demonstrated durable efficacy in patients with *RET*-driven cancers.[13-16] Selpercatinib's high *RET*-selectivity and low off-target activity are associated with fewer adverse events compared with non-*RET* kinases.[14] However, limited data are available on the long-term effects of selpercatinib on HRQoL from patients with *RET*-driven cancers.[4,17]

Patient-reported outcomes (PROs) include measures associated with HRQoL and symptom burden and are an important component of clinical trials to understand the effects of disease and associated treatments from the patient's perspective.[18-20] The LIBRETTO-001 trial, which is an ongoing, multicenter, global, phase I/II study of selpercatinib in patients with *RET*-driven cancers, included an exploratory objective to describe patient-reported changes from baseline in disease-related symptoms and HRQoL during selpercatinib treatment.[4,17] The interim analysis of PRO data (December 2019) showed that most patients with *RET* fusion-positive NSCLC or *RET*-mutated MTC remained stable or improved on all HRQoL subscales during selpercatinib treatment for ∼1 year.[4,17] Among patients with *RET* fusion-positive NSCLC, 61%-67% of patients experienced clinically meaningful improvements in GHS/QoL, 33%-61% in dyspnea scores, and 46%-63% in pain. Approximately 46% reported a decrease of ≥10 points in pain at cycle 3 versus baseline.[17] Among patients with *RET*-mutated MTC, 29% reported an improvement in GHS/QoL, and the median time to improvement was 5.6 months in patients naive to vandetanib/cabozantinib versus 3.6 months in those with prior vandetanib/cabozantinib treatment. Approximately 37% of the treatment-naive patients reported an improvement in diarrhea versus 51% for those with prior exposure to vandetanib/cabozantinib.[4]

This study adds to the existing interim findings from LIBRETTO-001 and assesses whether HRQoL was maintained or improved while on selpercatinib treatment for a longer duration in patients with *RET*-fusion-positive NSCLC, TC, TA, and *RET*-mutated MTC. The primary objective of this study was to descriptively summarize patient-reported disease-related symptoms and HRQoL during selpercatinib treatment including changes from baseline to 3 years (assessment cycle 37) for NSCLC and MTC and from baseline to 2 years (assessment cycle 25) for TC and TA. In addition, a secondary objective was to describe the patient-reported prevalence of diarrhea during selpercatinib treatment in the *RET*-mutated MTC cohort. Finally, as an exploratory objective, we evaluated the associations between tumor response, progression-free survival (PFS), and HRQoL.

PATIENTS AND METHODS

This *post-hoc* retrospective, descriptive study used data from the LIBRETTO-001 trial with a data cut-off date of 13 January 2023. The LIBRETTO-001 trial is being conducted at 89 sites in 16 countries among patients with *RET*-driven cancers. Eligible patients had disease progression on or after previous systemic therapies or no satisfactory therapeutic options and an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2. Details on the procedures followed in the trial are described elsewhere.[13,14,21] LIBRETTO-001 was conducted following Good Clinical Practice Guidelines and the Declaration of Helsinki, and all applicable country and local regulations. The trial protocol was approved by the institutional review board at each site and all the patients or guardians provided written informed consent.[13,14,21] Patient consent was waived as this was a noninterventional study based on the secondary use of data; therefore institutional review board approval was not required.

In this study, the NSCLC and TC cohorts included selpercatinib-treated patients who were naive to standard therapies or who had previously been treated with standard therapies. The MTC cohort comprised selpercatinib-treated patients who were naive to cabozantinib/vandetanib or were previously treated with these MKIs, and the TA cohort included heavily pretreated patients with nonlung, non-thyroid *RET* fusion-positive solid tumors. Patients completed the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) questionnaire version 3.0 (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103444).[4] This validated questionnaire is widely used in oncology clinical trials and has an overall GHS/QoL subscale, five functional domains (i.e. physical, role, cognitive, emotional, and social), three symptom domains (i.e. fatigue, pain, and nausea and vomiting), and six single-item symptom scales (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial impact). All QLQ-C30 subscales were scored from 0 to 100.[22] The previously published thresholds for clinical importance were used to interpret the QLQ-C30 scores in terms of clinically meaningful values. Scores lower than the thresholds of 83 (physical function), 75 (cognitive function), 71 (emotional function), or 58 (role and social function) on the functional subscales represent a clinically meaningful problem for patients. Conversely, scores higher than 50 (appetite loss, sleep disturbance, and constipation), 39 (fatigue), 25 (pain), 17 (diarrhea, dyspnea, and financial difficulties), or 8 (nausea/vomiting) represent clinically meaningful problems on the symptom subscales.[17,23]

Patients with *RET*-mutated MTC also completed a modified version of the Systemic Therapy-Induced Diarrhea Assessment Tool (mSTIDAT) at baseline (cycle 1, day 1, before study treatment), and every 8 weeks (or every other cycle) until cycle 13. The mSTIDAT assesses patient perceptions associated with diarrhea, its severity, daily number of bowel movements and diarrhea, presence of urgency,

abdominal discomfort, fecal incontinence, and QoL. It includes a subscale (scored from 0 to 10) on GHS/QoL that asks patients to rank the impact of bowel habits (3 items) and diarrhea (2 items) on their daily living.[24]

Patients who completed the QLQ-C30 questionnaire at baseline and at least once post-baseline were included in the PRO analyses. Compliance with the QLQ-C30 was calculated as the total number of patients who completed these questionnaires divided by the total number of patients on treatment at each visit. From baseline to year 3 (i.e. cycle 37) for the NSCLC and MTC cohorts and year 2 (i.e. cycle 25) for the TC and TA cohorts, scores on each subscale of the QLQ-C30 were reported descriptively as means and standard deviations (SDs). Changes from baseline for all items in the QLQ-C30 were calculated using mixed effect model repeated measures (MMRM) to allow incorporation of the longitudinal data structure and missing observations.

Changes in GHS/QoL or functional subscale scores were considered an improvement if they increased from baseline by $\geq$10 points or worsening if they decreased by $\geq$10 points. Conversely, a decrease from the baseline of $\geq$10 points in symptom subscale scores was considered an improvement, and an increase from the baseline of $\geq$10 points a worsening.[25] The proportion of patients with improved, stable, or worsening status for all subscales at year 3 for NSCLC and MTC and at year 2 for TC and TA post-baseline were reported. Other outcomes included duration of improvement, time to first improvement, and time to first worsening. Duration of improvement was defined as the time from the date of first improvement [e.g. an increase of $\geq$10 points from baseline for GHS and functioning subscales (or a decrease for symptom subscales)] to the date of first worsening [e.g. a decrease of $\geq$10 points for GHS and functioning subscales (or an increase for symptom subscales)] after improvement. Patients who did not have an event were censored at treatment discontinuation or the last evaluable disease assessment, whichever occurred first. Kaplan—Meier methods were used to report the median and 95% confidence interval (CI) for the time-to-event outcomes.

For the secondary objective, compliance with the mSTIDAT was calculated as the total number of patients who completed the questionnaire divided by the total number of patients on treatment at each visit. The compliance rate was described for patients who completed the baseline and at least one postbaseline evaluation and reported as means and SDs. The proportion of patients with diarrhea and its severity at baseline and at year 3 of selpercatinib treatment was reported.

For the exploratory objective, the association between GHS/QoL, functional domain subscales, and probability of response (complete response or partial response) was assessed using logistic regression. The Cox proportional hazards regression model evaluated the association between baseline GHS/QoL, functional domain subscales, and PFS.

Missing data were not imputed. All analyses were based on observed data only. The sample sizes at each assessment visit were based on the total number of patients with nonmissing data for the parameter of interest at that visit.

RESULTS

This study included 316 patients with *RET* fusion-positive NSCLC, 295 patients with *RET*-mutated MTC, 65 patients with *RET* fusion-positive TC, and 52 patients with *RET* fusion-positive TA (Table 1). The median (range) age of patients was 61.0 (23.0-92.0) years (NSCLC), 58.0 (15.0-90.0) years (MTC), 59.0 (20.0-88.0) years (TC), and 54.0 (21.0-85.0) years (TA). Over 90.0% had ECOG PS of 0/1 and over half of the patients were women except in the MTC cohort (39.0%). Of the 728 patients with *RET*-driven cancers, ~66.9% of patients received prior systemic therapy. The baseline assessment was completed by 63.3% of the patients in the NSCLC cohort, 70.8% in the MTC cohort, 76.9% in the TC cohort, and 73.1% of the patients in the TA cohort. The total compliance rate across all visits was 80.4% (NSCLC), 81.7% (MTC), 70.1% (TC), and 85.2% (TA; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103444).

RET fusion-positive NSCLC cohort

The mean GHS/QoL and physical function scores at baseline were 61.8 (SD 23.9) and 76.2 (SD 22.1) versus 69.3 (SD 17.4) and 83.5 (SD 17.8) at year 3, respectively (Supplemental Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103444). Approximately 85.1% of patients maintained or improved their QoL while on continuous selpercatinib treatment for 3 years (Figure 1). Most patients (83.3%) also maintained or improved physical function (Figure 2). Among other symptom subscales, 87.1% and 62.9% of patients maintained or improved fatigue and dyspnea at year 3 (Figure 3 and Supplementary Figures S2, available at https://doi.org/10.1016/j.esmoop.2024.103444). Other functional scores reported by patients in all cohorts are reported in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.103444. MMRM results showed no clinically meaningful improvements or worsening in GHS/QoL, functions, or symptoms in the NSCLC cohort (Supplementary Table S2 and Supplementary Figure S4 available at https://doi.org/10.1016/j.esmoop.2024.103444).

Among patients included in the time-to-event outcomes analyses for GHS/QoL, the median time to first improvement was 3.7 months (95% CI 2.1-5.5 months), duration of improvement was 5.6 months (95% CI 3.8-8.3 months), and time to first worsening was 19.1 months (95% CI 11.3-34.8 months). For physical function, the median time to first improvement was 18.5 months (95% CI 7.4-not estimable months), duration of improvement was 5.6 months (95% CI 3.8-7.6 months), and time to first worsening was 19.2 months (95% CI 13.8-31.3 months) (Table 2).

RET-mutated MTC cohort

The mean GHS/QoL and physical function at baseline were 64.9 (SD 23.4) and 80.2 (SD 20.7) versus 72.7 (SD 20.7) and

Table 1. Baseline patient characteristics

Variables	NSCLC (*N* = 316)	MTC (*N* = 295)	TC (*N* = 65)	TA (*N* = 52)
Age in years, median (range)	61.0 (23.0-92.0)	58.0 (15.0-90.0)	59.0 (20.0-88.0)	54.00 (21.0-85.0)
Sex, *n* (%)				
Male	133 (42.1)	180 (61.0)	32 (49.2)	25 (48.1)
Female	183 (57.9)	115 (39.0)	33 (50.8)	27 (51.9)
ECOG PS, *n* (%)				
0	115 (36.4)	111 (37.6)	25 (38.5)	16 (30.8)
1	190 (60.1)	167 (56.6)	36 (55.4)	32 (61.5)
2	11 (3.5)	17 (5.8)	4 (6.2)	4 (7.7)
Number of prior systemic regimens, *n* (%)				
0	69 (21.8)	116 (39.3)	24 (36.9)	5 (9.6)
1	72 (22.8)	95 (32.2)	10 (15.4)	12 (23.1)
2	68 (21.5)	42 (14.2)	8 (12.3)	20 (38.5)
≥3	107 (33.9)	42 (14.2)	23 (35.4)	15 (28.8)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; MTC, medullary thyroid cancer; *n*, number of patients in each subgroup; *N*, total number of patients in the population; NSCLC, advanced non-small-cell lung cancer; TA, tumor agnostic; TC, thyroid cancer.

85.7 (SD 19.0) at year 3, respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103444). After 3 years of continuous treatment with selpercatinib, 81.2% and 85.9% of patients had maintained or improved their QoL and physical function, respectively (Figures 1 and 2). In addition, 88.2% of patients had maintained or reported an improvement in diarrhea (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.103444) and 78.8% had maintained or improved fatigue (Figure 3). The MMRM results showed improvements in fatigue [least-squared (LS) mean −10.1, 95% CI −14.3 to −5.8], pain (LS mean −11.6, 95% CI −16.0 to −7.3), sleep disturbance (LS mean −14.5, 95% CI −19.6 to −9.4), and diarrhea (LS mean −29.1, 95% CI −33.8 to −24.4) at the end of year 3 from baseline (Supplementary Table S3 and Supplementary Figure S5 available at https://doi.org/10.1016/j.esmoop.2024.103444).

Concerning GHS/QoL, the median time to first improvement was 5.5 months (95% CI 3.7-7.3 months), duration of improvement was 5.6 months (95% CI 3.7-7.6 months), and time to first worsening was 30.4 months (95% CI 15.7-not estimable months). For physical function, the median time to first improvement was not estimable, duration of improvement was 9.2 months (95% CI 5.6-18.4 months), and time to first worsening was not estimable (95% CI 25.1 months-not estimable; Table 2).

Among the patients who completed the baseline and at least one postbaseline assessment of the mSTIDAT questionnaire, the compliance rate at baseline was 42.4% and 77.9% at year 3. The total compliance rate across all

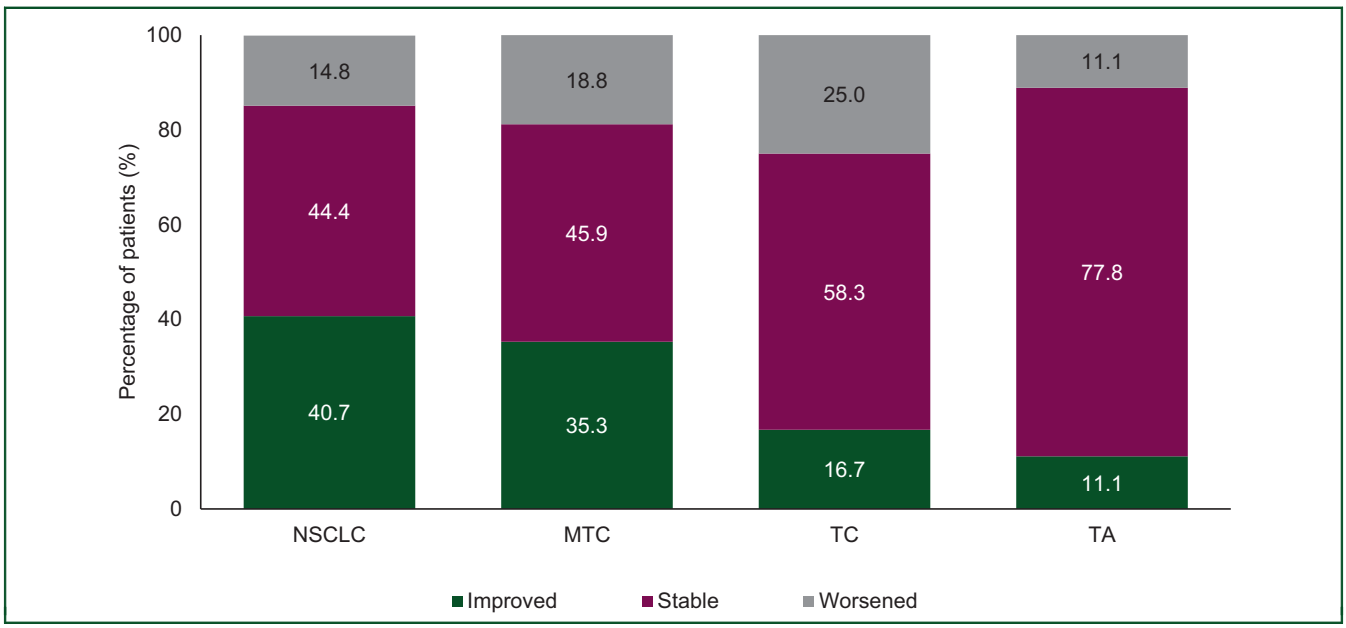

Figure 1. The proportion of *RET*-driven patients with improved, stable, and worsened global health status/QoL domain in the QLQ-C30 at year 3 (NSCLC and MTC cohorts) and year 2 (TC and TA cohorts).

MTC, medullary thyroid cancer; NSCLC, advanced non-small-cell lung cancer; QLQ-C30, Quality of Life Questionnaire-Core 30; QoL, quality of life; *RET,* rearranged during transfection; TA, tumor agnostic; TC, thyroid cancer.

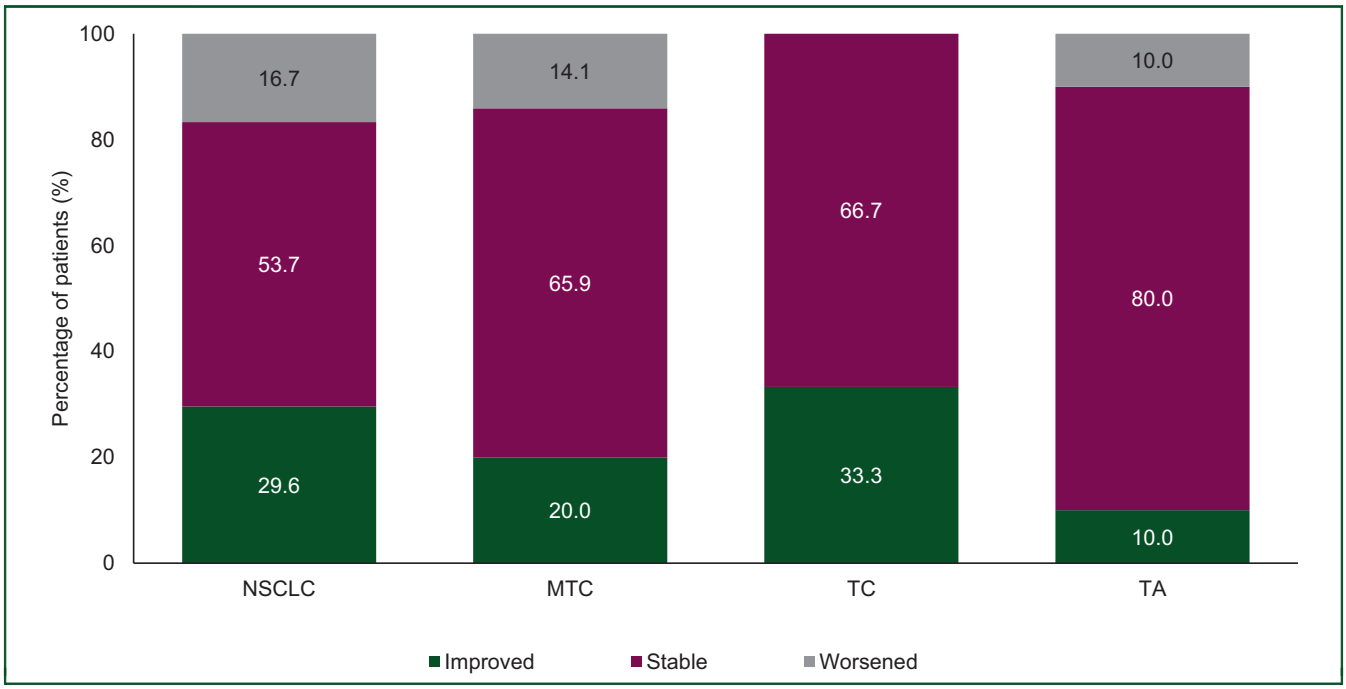

Figure 2. The proportion of *RET*-driven patients with improved, stable, and worsened physical function in the QLQ-C30 at year 3 (NSCLC and MTC cohorts) and year 2 (TC and TA cohorts).

MTC, medullary thyroid cancer; NSCLC, advanced non-small-cell lung cancer; QLQ-C30, Quality of Life Questionnaire-Core 30; *RET,* rearranged during transfection; TA, tumor agnostic; TC, thyroid cancer.

visits was 83.7% (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103444). Among the 42.4% of patients that completed the mSTIDAT questionnaire at baseline, 27.7% reported severe diarrhea, 47.5% reported moderate diarrhea, and 20.8% reported minimal diarrhea (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103444). After 3 years of continuous selpercatinib treatment, the proportion of patients with moderate or severe diarrhea reduced to 19.0% and 9.5%, respectively. Overall, the proportion of patients with MTC who reported diarrhea at year 3 decreased to 35.6% from 80.8% at baseline.

RET fusion-positive TC cohort

For GHS/QoL and physical function in the TC cohort, the mean score at baseline was 69.7 (SD 22.8) and 83.6 (SD 17.8) versus 77.8 (SD 11.4) and 91.7 (SD 8.1) at year 2 (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.103444). After 2 years of continuous selpercatinib treatment, 75.0% and 100.0% reported either maintaining or improving their QoL and physical function, respectively (Figures 1 and 2). In addition, ∼75.0% of patients either improved or maintained their fatigue and sleep disturbance from baseline (Figure 3 and Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.103444). MMRM results showed improvements in fatigue (LS mean −11.0, 95% CI −21.0 to −1.1) and dyspnea (LS mean −11.0, 95% CI −21.7 to −0.2) from baseline to the end of year 2 (Supplementary Table S6 and Supplementary Figure S6 available at https://doi.org/10.1016/j.esmoop.2024.103444).

Among patients who were included in the time-to-event outcomes analyses for GHS/QoL, the median time to first improvement was not estimable (95% CI 3.9 months-not estimable), duration of improvement was 2.8 months (95% CI 1.9-5.8 months), and time to first worsening was 7.5 months (95% CI 3.7-16.5 months). For physical function, the median time to first improvement was not estimable, duration of improvement was 6.9 months (95% CI 5.6-34.3 months), and time to first worsening was 16.5 months (95% CI 7.4-46.8 months) (Table 2).

RET fusion-positive TA cohort

In the TA cohort, the mean for GHS/QoL and physical function at baseline was 57.2 (SD 24.8) and 73.3 (SD 22.9) versus 74.1 (SD 16.4) and 91.3 (SD 8.4) at year 2 (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2024.103444). Approximately 89.0% reported maintaining or improving their GHS/QoL (Figure 1) and 90% maintained or improved their physical function (Figure 2) after 2 years of continuous selpercatinib treatment. Approximately 40% reported to have improved or maintained their fatigue (Figure 3) and all patients either improved or maintained their appetite loss (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.103444). MMRM results showed an improvement in appetite loss (LS mean −29.1, 95% CI −39.7 to −18.5) and pain (LS mean −10.6, 95% CI −23.7 to 2.5) at the end of year 2 from baseline (Supplementary Table S7 and Supplementary Figure S7 available at https://doi.org/10.1016/j.esmoop.2024.103444).

Table 2. Time-to-event outcomes in patients with *RET*-driven cancers

Domain	Subscales	NSCLC			MTC			TC			TA		
		TTFI	DOI	TTFW	TTFI	DOI	TTFW	TTFI	DOI	TTFW	TTFI	DOI	TTFW
Global health status/Quality of life		3.7 (2.1-5.5)	5.6 (3.8-8.3)	19.1 (11.3-34.8)	5.5 (3.7-7.3)	5.6 (3.7-7.6)	30.4 (15.7-NE)	NE (3.9-NE)	2.8 (1.9-5.8)	7.5 (3.7-16.5)	2.0 (1.9-5.3)	3.8 (2.8-22.4)	NE (24.9-NE)
Functional domain	Physical	18.5 (7.4-NE)	5.6 (3.8-7.6)	19.2 (13.8-31.3)	NE (NE-NE)	9.2 (5.6-18.4)	NE (25.1-NE)	NE (NE-NE)	6.9 (5.6-34.3)	16.5 (7.4-46.8)	4.2 (2.0-NE)	12.0 (3.7-NE)	NE (14.1-NE)
Symptom domains	Fatigue	3.7 (2.1-3.9)	2.9 (2.1-3.7)	9.2 (7.0-11.3)	3.7 (2.1-3.9)	3.6 (2.8-3.7)	12.0 (9.1-22.2)	5.5 (2.6-22.3)	3.7 (2.0-5.6)	5.6 (3.7-10.2)	2.0 (1.9-19.3)	12.0 (1.9-25.5)	11.1 (3.9-NE)
	Pain	3.9 (2.1-9.3)	5.6 (3.7-6.2)	13.8 (9.5-17.0)	3.9 (2.3-11.1)	3.7 (2.8-5.6)	16.5 (9.2-22.1)	9.2 (3.7-NE)	3.7 (1.9-4.7)	11.1 (3.7-24.0)	3.7 (1.9-NE)	3.7 (1.9-NE)	24.9 (5.8-NE)
Single-item symptom scales	Dyspnea	9.4 (3.7-NE)	5.6 (3.7-7.6)	44.2 (33.2-NE)	NE (NE-NE)	5.6 (3.7-12.0)	38.7 (19.5-NE)	16.8 (3.7-NE)	2.6 (1.9-4.6)	NE (38.0-NE)	NE (NE-NE)	1.9 (1.6-NE)	20.5 (13.7-NE)
	Appetite loss	NE (11.1-NE)	5.8 (4.6-9.5)	27.5 (16.1-42.4)	NE (NE-NE)	9.0 (5.6-14.8)	42.8 (31.0-NE)	NE (NE-NE)	28.2 (3.7-NE)	13.8 (5.6-36.1)	2.0 (1.9-NE)	NE (1.9-NE)	NE (30.4-NE)
	Sleep disturbance	19.4 (7.5-NE)	5.5 (3.7-5.8)	31.1 (19.1-NE)	6.5 (3.8-16.6)	4.1 (3.7-5.6)	29.5 (19.8-41.4	11.7 (3.7-NE)	2.8 (1.9-4.6)	19.4 (9.4-NE)	9.3 (3.7-NE)	5.8 (1.9-NE)	19.4 (13.7-NE)
	Diarrhea	NE (NE-NE)	2.8 (1.9-5.6)	7.5 (5.8-11.1)	3.3 (2.0-5.5)	12.0 (7.4-17.5)	NE (NE-NE)	NE (NE-NE)	1.9 (1.8-NE)	7.9 (3.8-18.5)	NE (3.7-NE)	3.9 (1.8-7.4)	11.1 (3.8-26.0)

Values reported are the median (95% confidence interval) number of months estimated with the Kaplan–Meier method and Greenwood formula. Only clinically relevant parameters were reported.
DOI, duration of improvement; MTC, medullary thyroid cancer; NE, not estimable; NSCLC, advanced non-small-cell lung cancer; *RET*, rearranged during transfection; TC, thyroid cancer; TTFI, time to first improvement; TTFW, time to first worsening.

For GHS/QoL, the median time to first improvement was 2.0 months (95% CI 1.9-5.3 months), duration of improvement was 3.8 months (95% CI 2.8-22.4 months), and time to first worsening was not estimable (95% CI 24.9 months-not estimable). For physical function, time to first improvement was 4.2 months (95% CI 2.0-not estimable months), duration of improvement was 12.0 months (95% CI 3.7-not estimable months), and time to first worsening was not estimable (95% CI 14.1-not estimable months; Table 2).

Exploratory analysis

In the MTC and TC cohorts, GHS/QoL was significantly associated with PFS [MTC—hazard ratio (HR) 0.89, 95% CI 0.81-0.97; $P = 0.01$ and TC—HR 0.78, 95% CI 0.62-0.98; $P = 0.03$]. In the NSCLC cohort, emotional function was associated with a higher probability of PFS (HR 1.13, 95% CI 1.01-1.28; $P = 0.04$), whereas cognitive function was associated with a lower probability of PFS (HR 0.88, 95% CI 0.78-0.99; $P = 0.04$). In the TC cohort, social function was associated with PFS (HR 0.63, 95% CI 0.41-0.98; $P = 0.04$); Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.103444).

There was no association between GHS/QoL and the probability of tumor response except the TA cohort where the odds of tumor response were high with improved physical function (odds ratio 9.39, 95% CI 2.03-43.34; $P = 0.004$). However, this estimate has higher uncertainty because of the wider confidence interval. Other functional domains did not show any association with tumor response across cohorts (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2024.103444).

DISCUSSION

HRQoL offers the potential to assess the psychological and physical effects of treatments from the patient's experience, enable shared decision making, and support the evaluation of the risks versus benefits of newer therapies.[26] There is limited research on long-term PROs for patients with *RET*-driven cancers who received selpercatinib. In this study, we used updated PRO data from the LIBRETTO-001 trial to describe long-term patient-reported symptoms, functioning, and HRQoL in *RET*-driven cancers. In addition, our data extend findings from prior studies[4,17] by describing PROs beyond those associated with HRQoL and in other *RET*-driven cancers not described before, such as *RET* fusion-positive TC and TA. The underlying hypothesis for this study was that patients treated with selpercatinib maintained their HRQoL while on treatment. Before the approval of selpercatinib, palliative chemotherapy (combination or monotherapy) was the primary treatment option available for patients with *RET*-altered cancers where HRQoL, on average, decreased.[27] Therefore showing that any patients maintained or improved their QoL over a 2- or 3-year period on treatment with selpercatinib is meaningful when

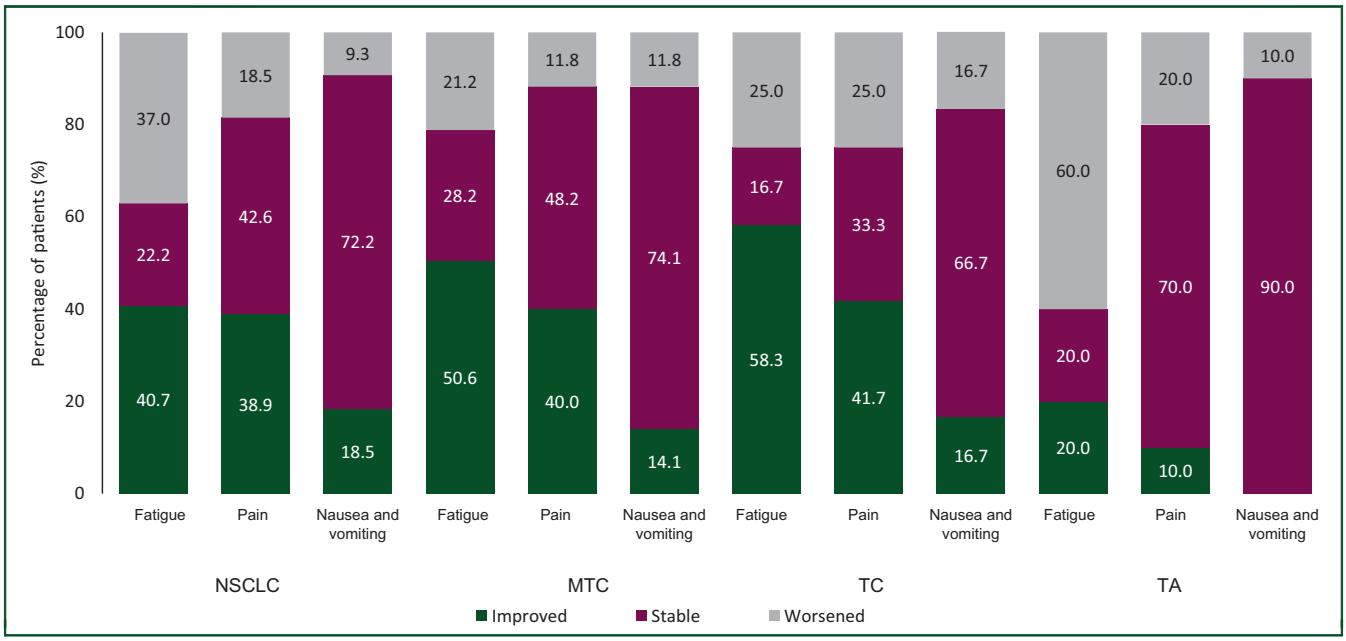

Figure 3. The proportion of *RET*-driven patients with improved, stable, and worsened symptom subscales in the QLQ-C30 at year 3 (NSCLC and MTC cohorts) and year 2 (TC and TA cohorts).

MTC, medullary thyroid cancer; NSCLC, advanced non-small-cell lung cancer; QLQ-C30, Quality of Life Questionnaire-Core 30; *RET,* rearranged during transfection; TA, tumor agnostic; TC, thyroid cancer.

compared with QoL reported with historical real-world oncology practice. As more precision medicine therapies become available, evaluating their impact on PROs will be important.

In our study, patients were compliant with PRO questionnaires; >80% of patients in the NSCLC and MTC cohorts and >70% of patients with TC and TA were compliant with the QLQ-C30 across all visits. Patients with *RET*-driven cancers experience a variety of symptoms during treatment, such as dyspnea, pain, insomnia, or fatigue (NSCLC); diarrhea (MTC); or gastrointestinal symptoms and appetite changes (TC), all of which are likely to affect HRQoL and functioning.[4,11,24,28] In this study, a majority of patients across most cohorts reported improved or stable outcomes for GHS/QoL, physical function, symptoms such as dyspnea, appetite loss, insomnia, and diarrhea, as well as fatigue and pain on selpercatinib treatment. Approximately 75% in the NSCLC cohort reportedly maintained or improved QLQ-C30 scores for GHS/QoL, symptom subscales, and functional domains at year 3, and 83% in the TC cohort reported the same at year 2. In the MTC and TA cohorts, ∼56% and 40% of patients reported improved or stable GHS/QoL, symptom subscales, and functional domain scores at the end of year 3 and year 2, respectively.

In the assessment of time-to-event outcomes, our study found that selpercatinib was associated with a short time-to-first improvement for QoL, functional, and symptom domains, ranging from ∼2 to 19 months across all cohorts. Furthermore, the median duration of improvement varied across cohorts ranging from 2 to 28 months. Dyspnea is a major symptom reported by patients with NSCLC.[29] In our study, between 85% and 95% of patients with NSCLC reported improvements or stable dyspnea at each assessment cycle through year 3. These findings are supported by an earlier PRO analysis of LIBRETTO-001 data.[17] Importantly, our study with long-term PRO data showed extended median duration of improvement for dyspnea from Minchom et al.[17] of 3.4 months to 5.6 months. In addition, our study also reported a longer median time to worsening of physical function (19.2 months) from another PRO study in Asian patients with NSCLC, where the median time to deterioration of physical function was 14 months.[30] In another paper that assessed PRO data from LIBRETTO-001, a lower proportion of selpercatinib-treated patients reported worsening symptoms versus the control group (23% versus 43%).[31] Findings associated with other symptoms such as pain, fatigue, and insomnia were similar to results reported in prior research[17]; in our study, >80% of patients with NSCLC reported improved or stable scores for these symptoms at each postbaseline assessment cycle.

In patients with MTC, where diarrhea is an important symptom affecting HRQoL, the duration of improvement was 12 months. One factor that could be attributed to the long duration of improvement for diarrhea in the MTC cohort could be the lower toxicity profile of selpercatinib versus other MKIs.[4] More than 80% of patients with MTC reported improved or stable diarrhea at each postbaseline assessment, and the proportion of patients reporting improved/stable diarrhea was ∼90% at year 3. In addition, the proportion of patients who reported experiencing diarrhea within 7 days of completing the mSTIDAT questionnaire decreased from baseline through year 3 and, beginning at cycle 15, less than half of the patients experienced diarrhea at year 3. These findings aligned with findings from another study reporting patient-reported diarrhea from LIBRETTO-001.[4] In their paper, Wirth et al.[4]

observed a reduction in diarrhea prevalence after baseline; however, a higher proportion of patients (14.3%) experienced severe diarrhea at the end of data availability (cycle 13). Furthermore, similar to their study, a majority of patients with MTC in our study reported improved or stable effects on appetite loss.[4]

The time to first worsening of QLQ-C30 measures was longer in the NSCLC and MTC cohorts, ranging from about 8 to 44 months, whereas it was shorter in the TC and TA cohorts (∼6 to 25 months). Approximately 50% of the TA cohort were patients with gastrointestinal cancers such as colorectal and pancreatic cancer, and our findings related to shorter time to first worsening highlight the unmet need for improved treatment in this population.

The interpretation of PRO data, however valuable, has limitations. The limitations attributed to PRO data from the LIBRETTO-001 clinical trial include the lack of a control arm. Because of the nature of the trial, changes from baseline were compared with a prespecified clinically important difference value and we acknowledge that changes from baseline can be caused by other factors than the treatment, including the absence of blinding of treatment, regression to the mean, or response shift. In addition, the majority (>50%) of the trial population consisted of pretreated patients, which may bias and magnify the QoL benefit. This limited the ability to infer the magnitude of causality for these PRO measures to treatment with selpercatinib. In addition, LIBRETTO-001 is still ongoing with a median time on treatment of 30.1 months for the overall population. As a result, some of the time-to-event analyses demonstrate the immaturity of data as medians or upper confidence intervals were not reached. As cycles of therapy progressed, the number of evaluable patients substantially decreased (particularly between 8 and 10 months) and subsequently, the stability of the data may have been less reliable. Furthermore, the QLQ-C30 was assessed at imaging and not at treatment cycles; some of the data collected were at interim data points which reduced the number of evaluations on the odd-cycled time points. An additional limitation was that multiplicity adjustment was not conducted as QoL was an exploratory endpoint. Finally, previous studies have shown a weak and nonsignificant correlation between HRQoL and PFS.[32,33] Findings assessing the relationship between HRQoL and PFS and tumor response were exploratory, unadjusted, and limited to baseline PRO scores. Consequently, the results of this exploratory analysis may not be generalizable to other tumor types and should be interpreted with caution.

Conclusions

PRO measures in LIBRETTO-001 were successfully incorporated with a high compliance rate across all visits for the QLQ-C30 (≥70%). In this analysis of PRO data, the majority of patients with *RET*-driven cancers remained stable or improved on most QLQ-C30 subscales at each study visit at 3 years for NSCLC and MTC and 2 years for TC and TA, demonstrating the favorable HRQoL during long-term treatment with selpercatinib.

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