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Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial.

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Contributors

VSu, SK, and AD were responsible for study design, provision of study materials, enrolment in clinical trials, data analysis, formal analysis, project administration, resources, and writing the original draft.

VSu, JWo, BK, HK, AS, JWe, MT, SK, and AD were responsible for data collection. VSu, JWo, JWe, SK, LS, and AD were responsible for data interpretation. VSu, JWo, SK, LS, and AD were responsible for writing conceptualisation of the manuscript. VSu, YO, SK, and AD were responsible for data curation. VSu, SK, KO, and AD were the principal investigators for this trial. VSu, BK, JWe, YO, SK, KO, VSo, SS, LS, JWr, and AD were responsible for writing, review, and editing of the manuscript. VSo, SS, and JWr were responsible for initial review of acquired data. JWo was responsible for critical revision. LS was responsible for methodology. VSu and AD verified the raw data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Interests

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HK and KO declare no competing interests.

Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial

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Summary

Background—Selpercatinib is a first-in-class, highly selective RET kinase inhibitor with CNS activity that has shown efficacy in RET fusion-positive lung and thyroid cancers. RET fusions occur rarely in other tumour types. We aimed to investigate the efficacy and safety of selpercatinib in a diverse group of patients with RET fusion-positive non-lung or thyroid advanced solid tumours (ie, a tumour-agnostic population).

Methods—LIBRETTO-001 is an ongoing phase 1/2, single-group, open-label, basket trial of selpercatinib in patients aged 18 years and older (or ≥12 years, where permitted by regulatory authorities) with *RET*-altered cancers. The trial is being conducted at 89 sites in 16 countries; the tumour-agnostic population was enrolled at 30 sites (outpatient and inpatient medical facilities) across eight countries. A prespecified interim analysis of LIBRETTO-001 was planned to investigate the efficacy and safety of selpercatinib in a tumour-agnostic population of patients with *RET* fusion- positive advanced solid tumours; the data cutoff date was Sept 24, 2021. Eligible patients had disease progression on or after previous systemic therapies or no satisfactory therapeutic options and an Eastern Cooperative Oncology Group performance status of 0–2. Selpercatinib was orally administered in a continuous 28-day cycle. Patients enrolled in the phase 1 dose-escalation portion received between 20 mg once daily or 20–240 mg twice daily; the phase 2 recommended dose was 160 mg twice daily. The primary endpoint was the objective response rate as determined by the independent review committee. The efficacy-evaluable tumour-agnostic population was defined as patients with *RET* fusion-positive cancer, other than non-small-cell lung cancer and thyroid cancer, who had at least 6 months of follow-up from the first study dose at the time of data cutoff (all responders at the time of data cutoff were followed up for at least 6 months from the onset of response unless they progressed or died earlier). Safety was analyzed in the tumour-agnostic population of patients who had been enrolled and received selpercatinib on or before the data cutoff date. This study is registered with ClinicalTrials.gov (NCT03157128) and is still recruiting participants.

Findings—Between Dec 4, 2017, and Aug 4, 2021, 45 patients with *RET* fusion-positive tumour-agnostic cancers were enrolled from the phase 1 dose-escalation and phase 2 dose-expansion cohorts of the trial. 43 (96%) of 45 patients received a starting dose of selpercatinib at the recommended dose of 160 mg twice daily. Of the two patients who did not, one received a dose of 160 mg twice daily via intra-patient dose escalation (as allowed per protocol for patients enrolled in the phase 1 portion of the study at lower doses) and the other patient's starting dose of 120 mg twice daily was never escalated. Of the 41 efficacy-evaluable patients, the objective response rate as per the independent review committee was 43·9% (95% CI 28·5–60·3; 18 of 41 patients). The most common grade 3 or worse treatment-emergent adverse events were hypertension (ten [22%] of 45 patients), increased alanine aminotransferase (seven [16%]),

and increased aspartate aminotransferase (six [13%]). Treatment-emergent serious adverse events occurred in 18 (40%) of 45 patients. No treatment-related deaths occurred.

Interpretation—Selpercatinib showed clinically meaningful activity in the *RET* fusion-positive tumour-agnostic population, with a safety profile consistent with that observed in other indications. Comprehensive genomic testing that includes *RET* fusions will be crucial for identifying patients who might benefit from selpercatinib.

Introduction

Genome-driven precision oncology has transformed the treatment landscape of many solid tumours. In recent years, some therapies have been recognized to yield clinically meaningful efficacy in the setting of a given biomarker, regardless of the underlying cancer type. This discovery led to several tissue-agnostic regulatory approvals, granted on the basis of the overall response and duration of response activity observed in single-group studies.[1,2] Approvals to date include anti-PD-1 antibodies for tumours harboring mismatch repair deficiency or microsatellite instability[1,3,4] or a high tumour mutational burden (≥10 mut/Mb),[5] as well as TRK inhibitors for *NTRK* fusion-positive tumours.[2,6] A common pattern associated with tissue-agnostic approvals is that the enrolling biomarker is present with a higher frequency in certain so-called anchor tumour types (the tumour types in which the qualifying alteration is most common), and much less commonly in a long tail of additional cancer types, a pattern also observed with *RET* fusions.

Research in context

Evidence before this study—We searched PubMed and major relevant congresses (the American Society of Clinical Oncology and the American Association for Cancer Research) up to May 9, 2022, using the search terms “RET”, “fusion or rearrangement”, “cancer”, and “treatment”. We did not restrict our search by publication date or language. Although conference proceedings, abstracts, and case reports reported that selective RET inhibitors, selpercatinib and pralsetinib, have activity in other *RET* fusion-positive cancers, no peer-reviewed publications of prospective clinical trials describing the tissue-agnostic efficacy of selective RET inhibitors were identified. Both drugs have been approved by multiple regulatory authorities for the treatment of *RET* fusion-positive lung and thyroid cancers in adolescent and adult patients.

Added value of this study—*RET* alterations are clinically validated actionable oncogenic drivers in lung and thyroid cancers, and selpercatinib has been shown to be beneficial for patients with these diseases. This study shows that *RET* fusions are oncogenic drivers in other cancers and that selpercatinib is a potentially effective treatment for *RET* fusion-positive cancers regardless of tumour type.

Implications of all the available evidence—The activity of selpercatinib in a broad variety of *RET* fusion-positive solid tumours is clinically meaningful, providing durable responses in patients previously treated with standard-of-care therapies, or for whom no standard of care exists. These findings emphasise the importance of broad-based genomic

profiling to identify patients with *RET* fusions who might benefit from selpercatinib treatment.

RET fusions result in constitutively active, ligand- independent activation of the RET pathway,7–11 and most commonly occur in 1–2% of cases of non-small-cell lung cancer (NSCLC) and 5–10% of cases of thyroid cancer (papillary thyroid or poorly differentiated thyroid cancer). Although these tumour types account collectively for the majority of *RET* fusion-positive cancers, *RET* fusions have also been observed in several other tumour types at a frequency of less than 1%, including cancers of the breast, colon, esophagus, ovary, prostate, stomach, pancreas, salivary gland, connective tissues, and histiocytic neoplasms.9,12–15 However, the activity of RET inhibition has not been systematically explored in these other tumours in a prospective basket trial.

Selpercatinib, a highly selective RET kinase inhibitor with CNS activity,16 was developed specifically to treat patients with *RET*-altered cancers. Selpercatinib is active preclinically in several *RET* fusion-positive models of lung, thyroid, and other cancers.17 Consistent with the hypothesis that *RET* fusions are targetable oncogenic drivers in NSCLC and thyroid cancer, selpercatinib showed notable efficacy in both treatment-naive and pretreated populations in a phase 1/2 study in patients with *RET*-altered advanced solid tumours (LIBRETTO-001).[18-21] These data led to the global regulatory approval of selpercatinib for *RET* fusion- positive lung and thyroid cancers.[22] Concurrently, LIBRETTO-001 enrolled a tumour-agnostic population of patients with *RET* fusion-positive advanced solid tumours. Here, we report the prespecified interim efficacy analyses of this tumour-agnostic population of patients with multiple *RET* fusion-positive cancers. This analysis, as agreed upon with the US Food and Drug Administration for submission for regulatory approval, was done after 40 evaluable patients were enrolled. The final results are anticipated to be published with a longer follow-up.

Methods

Study design and participants

LIBRETTO-001 was a phase 1/2, open-label, basket trial conducted at 89 sites (outpatient and inpatient medical facilities) in 16 countries. Of these, tumour-agnostic patients were enrolled at 30 sites (outpatient and inpatient medical facilities) in eight countries (Denmark, France, Germany, Israel, Japan, Singapore, Switzerland, and the USA; appendix pp 2-3). Complete eligibility criteria are summarized in the protocol (appendix p 11), as previously published.[23] Briefly, eligible patients were aged 18 years or older (or ≥12 years, where permitted by regulatory authorities), with evaluable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and a life expectancy of at least 3 months. Baseline disease assessment was based on radiographic tumour measurements done via CT or MRI. Previous analyses have described the results in patients with NSCLC and thyroid cancers.[18-21,23] Patients in the *RET* fusion-positive tumour-agnostic population with disease progression on or after previous systemic therapies or who had no satisfactory therapeutic options were eligible for this analysis. Local molecular testing was done in a certified laboratory to identify *RET* fusions by next-generation sequencing, fluorescent in- situ hybridization, or

PCR to identify an activating *RET* fusion or rearrangement in tumour or blood, with review and approval by the sponsor. Patients previously treated with another selective RET inhibitor were excluded.

The population discussed herein pooled patients from the phase 1 dose-escalation and phase 2 dose-expansion cohorts, including patients with *RET* fusion-positive solid tumours who progressed on or were intolerant to at least one previous standard therapy, patients with *RET* fusion- positive solid tumours who did not receive any previous standard first-line therapy, and patients who met the eligibility criteria but did not have measurable disease or who had *RET* fusion confirmation via circulating free DNA because no tissue sample was available.

The LIBRETTO-001 trial was done in accordance with Good Clinical Practice guidelines, in line with principles of the Declaration of Helsinki, and all applicable country and local regulations. The protocol was approved by the institutional review board or independent ethics committee at each investigative site. All patients provided written informed consent.

Procedures

Selpercatinib was orally administered in a continuous 28-day cycle until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients enrolled in the phase 1 dose-escalation cohort received between 20 mg once daily or 20–240 mg twice daily in the following doses: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg, 160 mg, 200 mg, and 240 mg of selpercatinib. The phase 2 recommended dose was 160 mg twice daily. Patients who had a dose reduction (one level to 120 mg twice daily or two levels to 80 mg twice daily) due to an adverse event were permitted to re-escalate upon resolution of the adverse event. Patients with progressive disease could continue treatment per investigator discretion of perceived clinical benefit with sponsor approval.

Radiological tumour assessments were done at baseline, every 8 weeks for 1 year, and every 12 weeks thereafter. Response was determined according to RECIST 1.1, assessed by both the investigator and independent review committee. All responses required a central confirmation of radiological assessment more than 4 weeks after the initial assessment of response. Adverse events were assessed from the first dose of study drug until the safety follow-up visit, 28 days after the last selpercatinib dose. The safety review committee met regularly to review safety data, including serious adverse events, fatal adverse events, and adverse events leading to treatment discontinuation. Adverse events were graded according to Common Terminology Criteria for Adverse Events (version 4.03). Standard laboratory safety assessments were completed per protocol.

Outcomes

The primary phase 2 endpoint was the objective response rate (complete response or partial response) assessed by the independent review committee per RECIST 1.1. Secondary endpoints reported in this Article are additional efficacy assessments of objective response rate by the investigator; clinical benefit rate (defined as the proportion of patients with a best overall response of complete response, partial response, or stable disease lasting ≥16 weeks) by the independent review committee and investigator; duration of response (defined as the time from the start date of complete response or partial response, whichever occurred

first, and was subsequently confirmed, to the first date that recurrent or disease progression was objectively documented) by the independent review committee and investigator; time to response (defined as the time between the date of the first study dose and the first documentation of confirmed objective response [complete response or partial response, whichever occurred earlier]) by the independent review committee and investigator; time to best response (defined as the time between the date of the first study dose and the first documentation of complete response or partial response, whichever was subsequently confirmed) by the independent review committee and investigator; progression-free survival (defined as the time between the date of the first study dose and the earliest date of documented disease progression or death, whichever occurred first) by the independent review committee and investigator; overall survival (defined as the time between the date of the first study dose and the date of death); and safety.

Because of the small sample size of the study, additional secondary endpoints of CNS objective response rate and CNS duration of response for this population were not analyzed. Furthermore, the pharmacokinetics of selpercatinib were largely derived from the overall study population (approximately 800 patients) and are therefore outside the scope of this Article.

Statistical Analysis

Sample size considerations for the overall population have been previously described.[23]

As per the statistical analysis plan (appendix p 11), and as agreed with the US Food and Drug Administration, the planned sample size for this prespecified analysis was approximately 40 patients from phase 1 and phase 2 with documented *RET* fusion-positive cancer who had received at least one dose of selpercatinib by March 24, 2021. Assuming the true objective response rate of 40%, the planned sample size was estimated to provide approximately 79% power to reject the null hypothesis that the true objective response rate is 20% or lower, with a two-sided alpha of 5%. Ruling out a lower limit of 20% for objective response rate is considered clinically meaningful when compared with available treatment options. The efficacy-evaluable tumour-agnostic population was defined as patients with *RET* fusion-positive cancer, other than NSCLC and thyroid cancer, who had at least 6 months of follow-up from the first study dose at the time of data cutoff (all responders at the time of data cutoff were followed up for at least 6 months from the onset of response unless they progressed or died earlier). The data cutoff date was Sept 24, 2021. Safety was analyzed in the tumour-agnostic population of patients who had been enrolled and received selpercatinib on or before the data cutoff date.

95% CIs for response rates were calculated with the Clopper-Pearson method. Supportive subgroup analyses were done to assess the response across different tumour types. All time-to-event endpoints were estimated with the Kaplan-Meier method, with 95% CIs calculated using the Brookmeyer and Crowley method. Median follow-up was estimated according to the reverse Kaplan-Meier estimate of potential follow-up.[24] Prespecified landmark analyses of progression-free survival at 1 year and 2 years, and overall survival at 1 year, 18 months, and 2 years were done.

A post-hoc analysis for response by fusion partner was also done. In addition to the efficacy and safety analyses, an exploratory ad-hoc intra-patient sensitivity analysis was done to compare best overall response from the last line of previous systemic therapy received before enrolment in LIBRETTO-001 with investigator-assessed best overall response on selpercatinib, with each patient serving as their own control. The best overall response to the last previous therapy was collected retrospectively and based on patients' medical records, in contrast to best overall response to selpercatinib treatment, which was assessed prospectively by the investigator by use of RECIST 1.1. The McNemar exact test was done to assess the significance of the difference between response rates. The Sankey diagram was used to visualize a change from last previous therapy to the best overall response to selpercatinib for each patient. In an additional exploratory analysis, the Growth Modulation Index (GMI) was calculated as the ratio of time spent on selpercatinib treatment to time spent on last previous therapy. A GMI greater than 1·33 is considered as a marker of meaningful clinical activity of a new treatment.[25] This exploratory analysis was done in 37 patients who had received systemic therapy before enrolment in LIBRETTO-001. All statistical analyses were done with SAS (version 9.1.2). This study is registered with ClinicalTrials.gov (NCT03157128).

Role of the funding source

This study was jointly designed by the funder and the investigators. The funder of the study had a role in study design, data collection, data analysis, data interpretation, and in the writing, revision, and approval of the manuscript.

Results

Between Dec 4, 2017, and Aug 4, 2021, 806 patients were enrolled into LIBRETTO-001, of whom 45 comprised the *RET* fusion-positive tumour-agnostic population (figure 1). Patients with 14 unique tumour types were treated (table 1). Overall, 26 (58%) of the 45 enrolled patients had refractory gastrointestinal malignancies; other histologies included salivary, breast, sarcoma, xanthogranuloma, carcinoid, ovarian, pulmonary carcinosarcoma, and carcinoma of the skin. Patients had received a median of two previous systemic therapies (IQR 1·0–3·0), with 14 (31%) of 45 patients having received three or more previous systemic lines of therapy. 37 (82%) patients had previously received chemotherapy. Five (11%) had previously received multikinase inhibitors with some activity against RET kinase. The majority of *RET* fusions were identified with next-generation sequencing. The most common fusion partner identified was *NCOA4* (in 17 [38%] patients; table 1). One patient with colorectal cancer had micro- satellite instability-high (MSI-H) status before enrollment. 43 (96%) of 45 patients received a starting dose of selpercatinib at the recommended dose of 160 mg twice daily. Of the two patients who did not, one received a dose of 160 mg twice daily via intra-patient dose escalation (as allowed per protocol for patients enrolled in the phase 1 portion of the study at lower doses) and the other patient's starting dose of 120 mg twice daily was never escalated.

41 (91%) of 45 patients were included in the efficacy analyses. Four patients were excluded because they did not meet the criteria for follow-up time (received the first dose after March 24, 2021). 24 (59%) of 41 patients had gastrointestinal malignancies. The objective response

rate per independent review committee and investigator assessment was 43·9% (95% CI 28·5–60·3; 18 of 41 patients; table 2). As per both the independent review committee and investigator, a complete response was attained in two (5%) of 41 patients (table 2; figure 2C). The clinical benefit rate was 63·4% (95% CI 46·9–77·9; 26 of 41 patients) as per the independent review committee and investigator. Responses were observed in all histologies in which two or more patients were enrolled, and in four of seven histologies with one patient enrolled (table 3). The patient with colorectal cancer and MSI-H status had a best response of stable disease as per both the independent review committee and investigator. The median duration of response was 24·5 months (95% CI 9·2–not evaluable [NE]) as per the independent review committee and 18·4 months (9·2–NE) as per the investigator (table 2; figure 3A, B). The median time to response was 1·9 months (IQR 1·7–2·0) as per both the independent review committee and investigator.

The median time to best response was 1·9 months (IQR 1·8–2·0) as per the independent review committee and 1·9 months (1·8–3·5) as per the investigator. The objective response rate and duration of response by fusion partner are provided in the appendix (p 4).

The median progression-free survival was 13·2 months (95% CI 7·4–26·2) as per the independent review committee and 11·1 months (5·6–19·1) as per investigator assessment (table 2). The estimated proportion of patients who were alive and progression-free at 1 year was 53·1% (95% CI 34·1–68·8) by independent review committee assessment and 43·1% (25·5–59·6) by investigator assessment. The median overall survival was 18·0 months (95% CI 10·7–NE); the estimated proportion of patients alive at 18 months was 51·7% (95% CI 32·9–67·6).

At the time of data analysis, 18 (44%) of 41 patients remained on selpercatinib treatment. The median duration of treatment was 11·0 months (95% CI 3·7–NE). Overall, 11 (27%) of 41 patients received selpercatinib treatment beyond progression on the basis of continued clinical benefit (appendix p 5). Therapies received after the study are shown in the appendix (p 6).

In the exploratory ad-hoc intra-patient analysis of best overall response based on investigator assessment, responses to selpercatinib were seen in 17 (46%) of 37 patients who had previously received systemic therapy. Three of these 17 patients who had responses to selpercatinib also responded to previous therapy. The objective response rate for selpercatinib was substantially higher than the objective response rate for the last previous therapy (in seven [19%] of 37 patients), regardless of the type of previous therapy received (appendix pp 7-8).

In an additional exploratory analysis, a GMI was calculated for each patient (appendix pp 7-8). In 26 (70%) of 37 patients, GMI was greater than 1·33. In a sensitivity analysis in which patients who received selpercatinib beyond progression were considered to have an event at the time of progression, 25 of 37 patients had a GMI >1·33). Notably, treatment was ongoing in 15 (41%) of these 37 patients, including two of nine patients with a GMI less than 1.

In the *RET* fusion-positive tumour-agnostic safety population (n=45), the safety profile was consistent with that of previous reports,[26] with no new safety signals identified compared to the full safety population (appendix p 9). Dose reductions occurred in 14 (31%) of 45 patients. Treatment-related adverse events leading to permanent selpercatinib discontinuation were observed in one (2%) patient (increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, and drug-induced liver injury)

Treatment-emergent adverse events that occurred during study treatment, regardless of causality, in addition to adverse events that were deemed to be related to selpercatinib as per the investigator, are shown in table 4. The most common grade 3 or worse treatment- emergent adverse events were hypertension (ten [22%] of 45), increased alanine aminotransferase (seven [16%]), and increased aspartate aminotransferase (six [13%]). Overall, grade 5 treatment-emergent adverse events were observed in three (7%) patients, with no grade 5 adverse events deemed to be related to treatment as per the investigator. Treatment-emergent serious adverse events occurred in 18 (40%) of 45 patients, including three (7%) deemed to be related to selpercatinib. Abdominal pain, nausea, pyrexia, and vomiting (each occurring in two [4%] of 45 patients) were the most common treatment-emergent serious adverse events. Drug-induced liver injury, fatigue, and hypersensitivity (each occurring in one [2%] of 45 patients) were the most common treatment-related serious adverse events.

Discussion

In this prespecified analysis, selpercatinib was found to be active in a tumour-agnostic population, including a diverse range of *RET* fusion-positive tumours, including histiocytic neoplasms (xanthogranuloma), epithelial neoplasms (gastrointestinal, breast, ovarian, skin, and carcinoid tumours), and mesenchymal tumours (soft tissue sarcoma). The efficacy of selpercatinib in this single-arm study was further supported by the intra- patient analyses comparing best response attained on previous therapy to best response observed with selpercatinib, in which overall response and time on treatment were both shown to be improved with selpercatinib.

Durable benefit was achieved with selpercatinib despite the heterogeneous, highly refractory, and heavily pretreated patient population.[27-32] More than 90% of patients had received one to three previous lines of systemic therapy), including chemotherapy, multikinase inhibitors, and immunotherapy. The objective response rate was 43·9%, and most patients with measurable disease had target lesion regression with therapy. Clinically meaningful improvements were observed for the secondary endpoints of duration of response and progression-free survival with selpercatinib; however, these median point estimates remain immature. This observed efficacy is particularly noteworthy given that 24 (59%) of 41 patients enrolled had gastrointestinal malignancies, a subset of solid tumours for which efficacy has rarely been shown with targeted therapies.

As the objective response rate of a population of heavily and heterogeneously pretreated patients with mixed tumour histologies might not convey the full extent of the efficacy

of selpercatinib (eg, previous response rates can vary substantially by tumour type), an exploratory analysis was done to compare the best overall response of selpercatinib to the patient's last therapy. This analysis showed a higher objective response rate with selpercatinib compared with patients' last therapy. Additionally, the anticipated duration of disease control can vary greatly by tumour type and even from patient to patient within the same tumour type. Therefore, time-to-event endpoints such as progression-free survival can be difficult to interpret in a population of mixed tumour types. To address this limitation, as an additional supportive exploratory analysis, a GMI was calculated for each patient. The GMI data for the entire dataset provide additional supportive evidence of benefit, showing that time on selpercatinib therapy exceeded the time on the last previous therapy in the majority of patients. Notably, GMI analysis is derived from the total time on treatment, including treatment after progressive disease, which is allowed according to the study protocol; however, this analysis is generally reflective of real-world practice for patients with limited treatment options, and data about the timing of progressive disease on the most recent treatment were not available. Both the best overall response and GMI analyses were exploratory in nature and therefore the results should be interpreted with caution.

Numerous factors can contribute to the varying objective response rates of different tumour histologies. Notably, of the two highest enrolling tumour types in this analysis, colorectal cancer appears to have a lower response rate (objective response rate of 20·0% as per the independent review committee) compared with pancreatic cancer (objective response rate of 54·5% as per the independent review committee). Although cross- trial comparisons should be made with caution, the response rate for patients with colorectal cancer observed in our study compares favourably with the objective response rate of approved agents in colorectal cancer (eg, 1·0% for regorafenib and 1·6% for tipiracil).[33,34] Furthermore, as evidenced by the median duration of treatment (9·2 months) for patients with colorectal cancer in our study, the objective response rate might not be the most appropriate measure of benefit for all diseases represented in this study.

Genetic diversity in colon cancer might also play a role in the lower rate of responses to selpercatinib in *RET* fusion-positive colon cancers. Previous small retro- spective case series have suggested that *RET* fusion- positive colorectal cancers are significantly associated with MSI-H status (48% in *RET* fusion-positive patients *vs* 7% in *RET* fusion-negative patients, p<0·001), with an independent poor prognostic impact on survival (median overall survival 14·0 months *vs* 38·0 months, hazard ratio 4·59 [95% CI 3·64–32·66]; p<0·001).[10] *NTRK* fusions have also previously been associated with MSI-H cancers in frequencies higher than *RET* fusions (*NTRK1*: nine [41%] of 22 patients; *NTRK3*: five [23%] of 22 patients; *RET*: two [9%] of 22 patients).[35] Additionally, targetable kinase fusions in *BRAF*/*RAS* have been previously observed with high frequency in MSI-H colorectal cancer.[36] In our study, only one patient with colorectal cancer had MSI-H status before enrolment, and stable disease was achieved as the best overall response. However, because tissue samples were not required immediately before enrolment or after disease progression, it is unknown whether the tumours from most patients who did not respond expressed one of these known resistance mechanisms or whether the tissue samples would have revealed other reasons for the absence of response. Further analysis of MSI-H status in *RET* fusion-positive colon cancer is warranted as this might have implications for the possible future approach of

multimodality treatment regimens including RET- targeted therapy and immune checkpoint inhibitor therapy. Along with *RET* fusions, some tumour types might also carry more genomic complexity than others. Inherent RAS-mediated primary resistance and acquired MAPK pathway resistance in patients treated with selpercatinib have been previously described.[37] Ongoing biomarker analyses for LIBRETTO-001 might provide additional clues about the mechanisms of primary and secondary resistance.

A limitation of the current study is that the patient population was derived from a non-randomized, single- group trial with no comparator. *RET* fusions are relatively rare, resulting in a heterogeneous population with a diversity of tumour types and relatively small numbers of patients with specific types of solid tumours. At this point in the study, follow-up times are also short.

The safety profile of the *RET* fusion-positive tumour- agnostic population was consistent with the safety profile previously observed in the full population of LIBRETTO-001. Most adverse events were of a low grade and the rate of drug discontinuation for treatment-related adverse events was low, at 2%. Overall, these data support the safety and efficacy of selpercatinib in patients with *RET* fusion-positive solid tumours, regardless of cause.

The LIBRETTO-001 study continues to enroll patients with *RET* fusion-positive solid tumours other than lung or thyroid tumours. The data generated by this programme thus far, in addition to the previously reported activity of selpercatinib in *RET* fusion-positive lung and thyroid cancers, provide clinical proof of concept that *RET* fusions are both central to oncogenesis and therapeutic- cally actionable across diverse tumour lineages, thus positioning selpercatinib as a tumour-agnostic therapy. This observation reiterates the importance of considering molecular profiling across a broad range of tumour types. Finally, only two targeted therapy regimens (TRK inhibitors for *NTRK* fusions and dabrafenib plus trametinib for $BRAF^{V600E}$)[2,38-40] are currently approved in a tumour-agnostic population. Although direct comparisons with previous studies should be made with caution, the objective response rate with second-line larotrectinib was 79% per investigator assessment and median progression-free survival was 28·3 months,[41] the objective response rate was 61% with entrectinib and median progression-free survival was 13·8 months,[38] the objective response rate was 41% with dabrafenib plus trametinib,[42] and the objective response rate with selpercatinib per investigator assessment was 44% and median progression- free survival was 11·1 months (13·2 months per independent review committee). It is worth noting the variation in the tumour types included for these separate analyses. So-called anchor tumour types of NSCLC and thyroid cancer made up a large proportion of the population in both analyses with larotrectinib and entrectinib, with a long tail of less common additional cancer types, each making up a very small proportion of the population analyzed. However, the patient population discussed here included only the long list of tumour types from LIBRETTO-001. Previously observed responses in the anchor tumour types from LIBRETTO-001 showed potent responses with selpercatinib in both *RET* fusion-positive NSCLC (objective response rate of 70% in the second-line setting or higher; objective response rate of 90% in the first-line setting)[23] as well as *RET* fusion- positive thyroid cancer (objective response rate of 79% in the second-line setting or higher; objective response rate of 100% in the first-line setting).[21,26] This seminal study of selpercatinib

therefore adds to a growing body of literature showing that the basket trial approach to targeted therapy development is feasible in diverse contexts, uncovers insights into the therapeutic actionability of an alteration across cancer types at enrollment, and provides access to under-served patient groups for whom standalone histology-specific trials are not feasible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing

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 USA 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 on Vivli – Center for Global Clinical Research Data.

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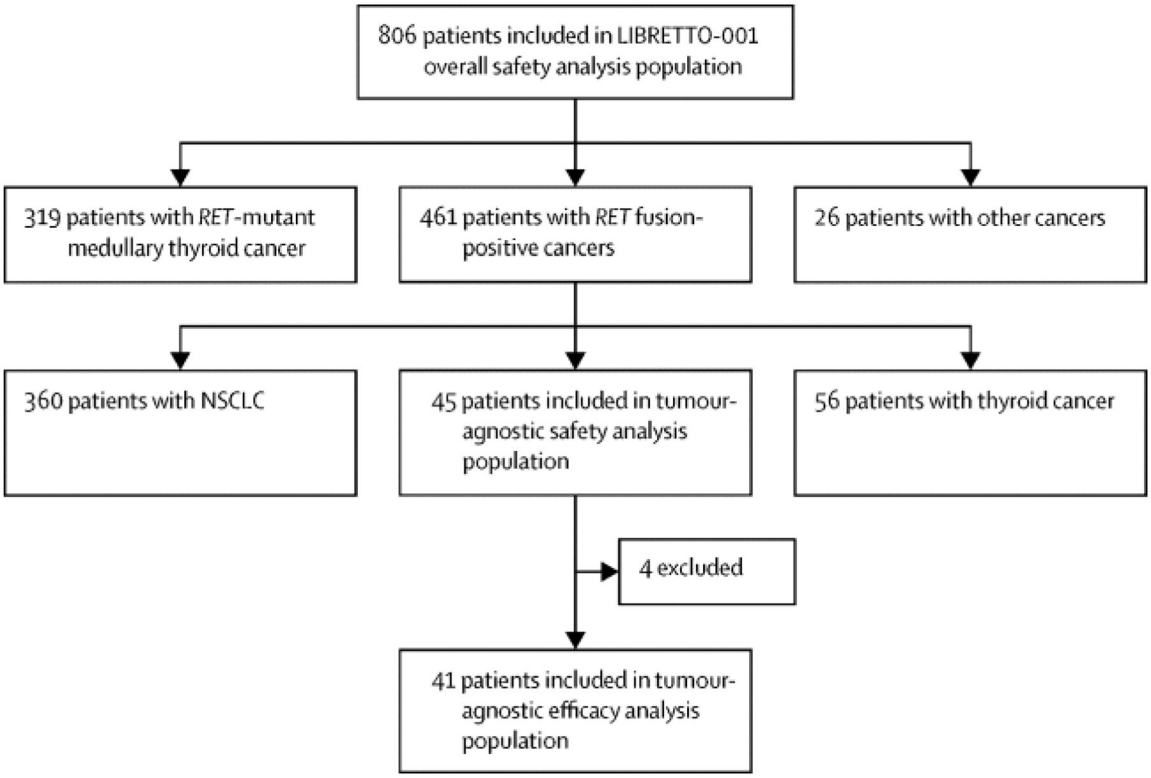
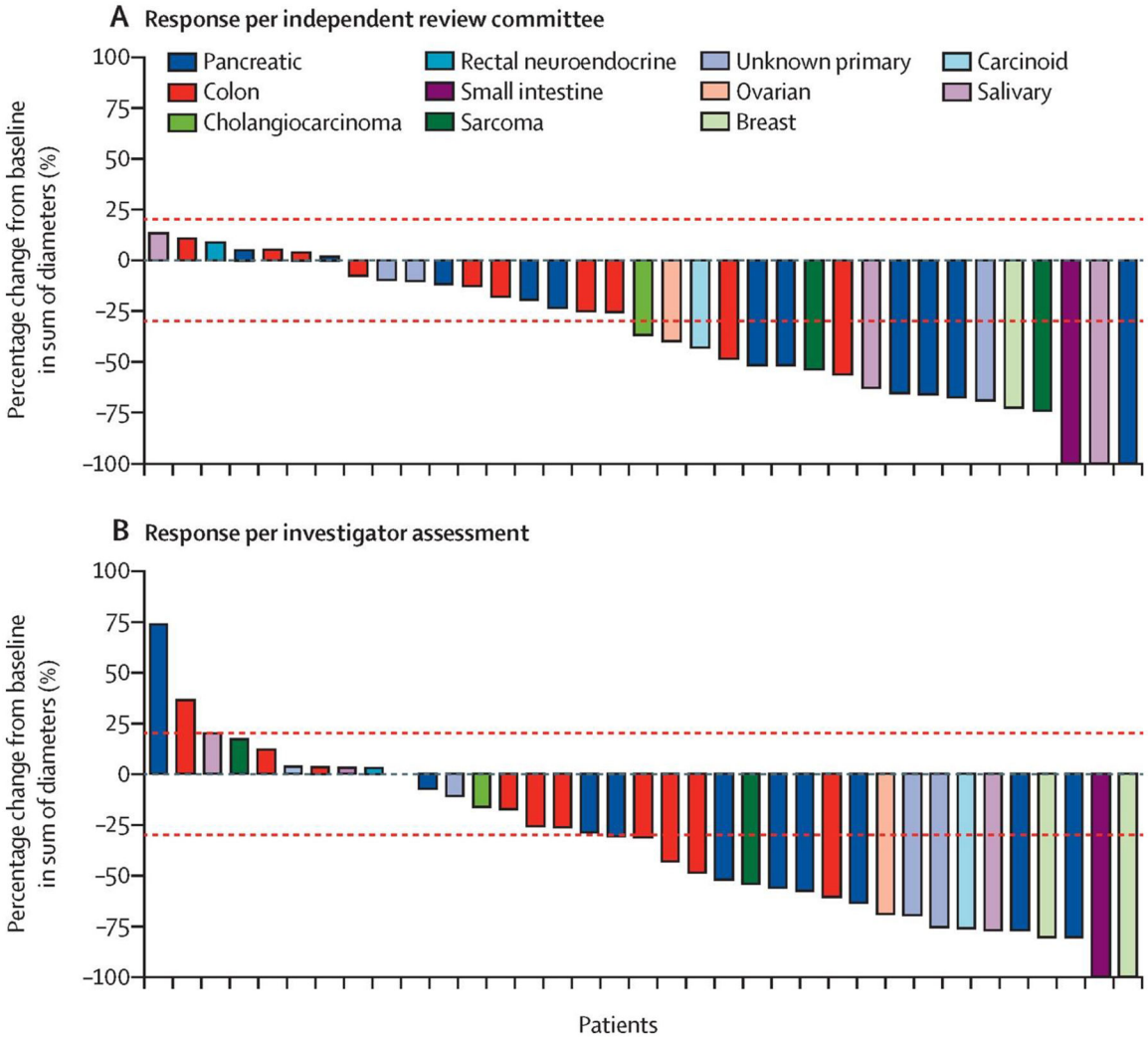


Figure 1. Trial Profile

Four patients were excluded from the efficacy-evaluable population because they did not meet the criteria for follow-up time (received the first dose after March 24, 2021). NSCLC=non-small-cell lung cancer.



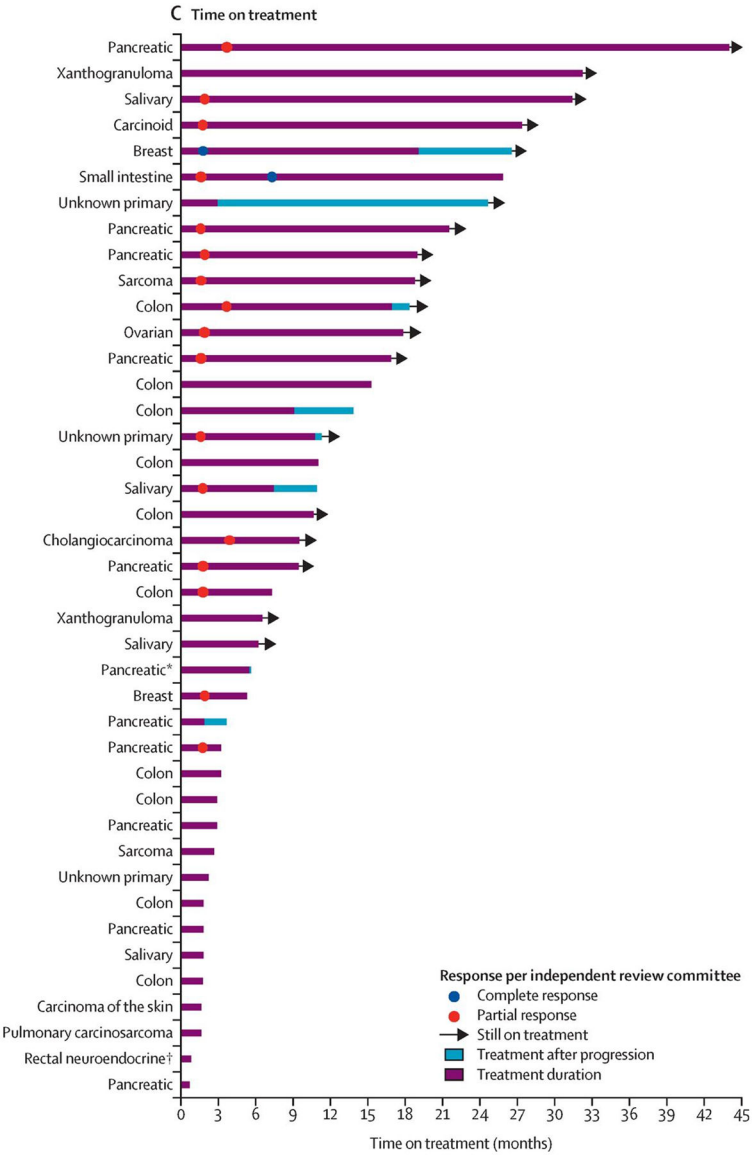


Figure 2. Response to selpercatinib

(A) Waterfall plot of maximum change in tumour size for the 35 evaluable patients with RET fusion-positive solid tumours as per the independent review committee. (B) Waterfall plot of maximum change in tumour size for the 35 evaluable patients with RET fusion-positive solid tumours as per investigator assessment. Vertical bars represent the best percentage change from baseline in the sum of diameters for all target lesions. Progressive disease (+20%) and partial response (–30%) are indicated with dashed lines. The waterfall plot excludes patients with no measurable disease (n=5) or no post-baseline lesion measurements (n=1). Two patients (one with pancreatic and one with salivary cancer) who had a 100% reduction in measurable target lesions were determined to have an overall partial response. One additional patient with breast cancer had no measurable disease (not shown on the plot) and was determined to have a complete response. (C) Time on treatment. The swimmer plot depicts duration of treatment and time to response in patients as per

the independent review committee. The time at which the first response was observed is indicated with circles. *Starting dose: 80 mg twice daily. †Starting dose: 120 mg twice daily.

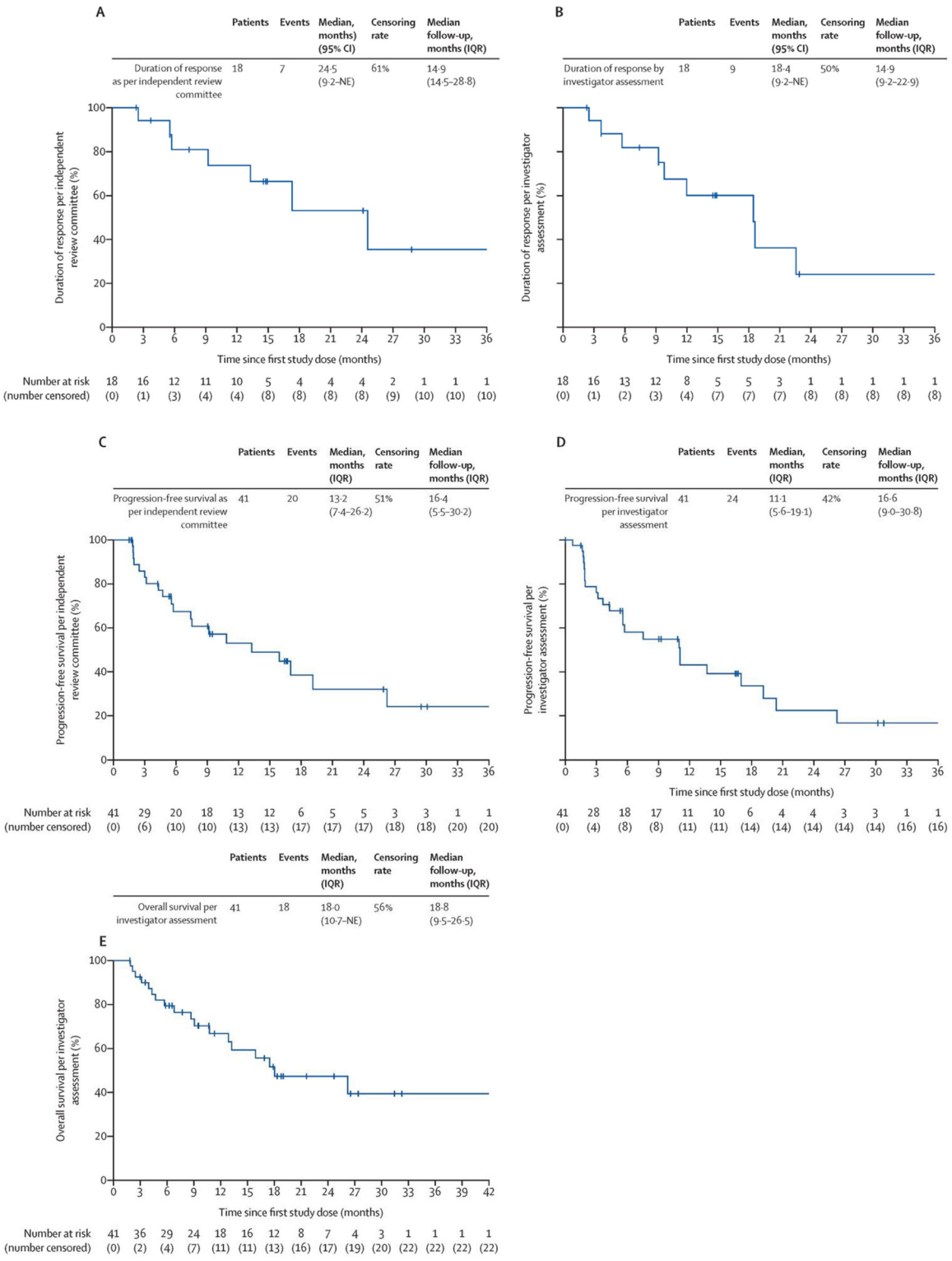


Figure 3. Kaplan-Meier plots

(A) Duration of response per independent review committee. (B) Duration of response per investigator. (C) Progression-free survival per independent review committee. (D)

Progression-free survival per investigator. (E) Overall survival per investigator. Tick marks indicate censored data. NE=not evaluable.

Table 1.

Baseline patient characteristics

	RET fusion tumour-agnostic population (n=45)
Age, years	53 (41·0–67·0)
Sex	
Female	23 (51%)
Male	22 (49%)
Race *	
White	31 (69%)
Asian	11 (24%)
Black or African American	2 (4%)
Other	1 (2%)
ECOG performance status score	
0	15 (33%)
1	27 (60%)
2	3 (7%)
Primary tumour diagnosis	
Pancreatic	12 (27%)
Colon	10 (22%)
Salivary	4 (9%)
Sarcoma	3 (7%)
Unknown primary	3 (7%)
Breast	2 (4%)
Carcinoma of the skin	2 (4%)
Cholangiocarcinoma	2 (4%)
Xanthogranuloma	2 (4%)
Carcinoid	1 (2%)
Ovarian	1 (2%)
Pulmonary carcinosarcoma	1 (2%)
Rectal neuroendocrine	1 (2%)
Small intestine	1 (2%)
Previous lines of systemic therapy	2·0 (1·0–3·0)
0	4 (9%)
1–2	27 (60%)
≥3	14 (31%)
Previous treatment regimen	
Chemotherapy	37 (82%)
Platinum-based chemotherapy	32 (71%)
Taxane chemotherapy	8 (18%)
Immunotherapy	7 (16%)
Anti-PD-1 or anti-PD-L1 therapy	7 (16%)

	RET fusion tumour-agnostic population (n=45)
Multikinase inhibitor[†]	5 (11%)
Other[‡]	15 (33%)
Previous radiotherapy	17 (38%)
Previous surgery	27 (60%)
Stage at initial diagnosis	
II	1 (2%)
III	3 (7%)
IV	38 (84%)
Missing	3 (7%)
History of metastatic disease	43 (96%)
Fusion partners[§]	
NCOA4	17 (38%)
CCDC6	7 (16%)
KIF5B	4 (9%)
RET gene rearrangement (FISH)	3 (7%)
Other	14 (31%)
Months since initial diagnosis (IQR)	15·6 (6·3–25·5)
Measurable disease (by investigator assessment)	40 (89%)
Measurable disease (by independent review committee)[¶]	36 (80%)

Data are n (%) or median (IQR). Percentages might not total 100% because of rounding. ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in-situ hybridisation.

[*] Race was reported by the patients. Other races included Native Hawaiian or other Pacific Islander.

[†] Multikinase inhibitors administered included cabozantinib, regorafinib, and anlotinib. Patients could have received more than one multikinase inhibitor.

[‡] Other previous systemic therapies included radioactive iodine, mTOR inhibitors, EGFR inhibitors, VEGF or VEGFR inhibitors, hormonal therapies, and selective RET inhibitors.

[§] Other *RET* fusion partners included *ETV6, TRIM24*, *ERC1, GOLGA5, GPHN, PRKAR1A*, *RASAL2*, *CGNL1*, *SPECC1L*, *TAF3*, *TFG*, and *TRIM33*.

[¶] Four patients were not assessed by the independent review committee since they were not part of the efficacy-evaluable population.

Table 2.

Efficacy analysis of patients with *RET* fusion-positive solid tumours (n=41)

	Independent review committee assessment	Investigator assessment
Objective response rate (95% CI)	43·9% (28·5–60·3)	43·9% (28·5–60·3)
Best response		
Complete response	2 (5%)	2 (5%)
Partial response	16 (39%)	16 (39%)
Stable disease	14 (34%)	13 (32%)
Progressive disease	3 (7%)	7 (17%)
Not evaluable	6 (15%)	3 (7%)
Duration of response (n=18)		
Median, months (95% CI)	24·5 (9·2–NE)	18·4 (9·2–NE)
Censoring	11 (61%)	9 (50%)
Median duration of follow-up, months (IQR)	14·9 (14·5–28·8)	14·9 (9·2–22·9)
Progression-free survival		
Median, months (95% CI)	13·2 (7·4–26·2)	11·1 (5·6–19·1)
Censoring	21 (51%)	17 (42%)
Median duration of follow-up, months (IQR)	16·4 (5·5–30·2)	16·6 (9·0–30·8)
1-year progression-free survival (95% CI)	53·1% (34·1–68·8)	43·1% (25·5–59·6)
2-year progression-free survival (95% CI)	32·1% (14·0–51·7)	22·4% (8·0–41·2)
Overall survival		
Median, months (95% CI)	..	18·0 (10·7–NE)
Censoring	..	23 (56%)
Median duration of follow-up, months (IQR)	..	18·8 (9·5–26·5)
1-year overall survival (95% CI)	..	66·8% (48·6–79·8)
2-year overall survival (95% CI)	..	47·4% (28·7–64·0)

Data are n (%), unless otherwise stated. Percentages might not total 100 because of rounding. NE=not evaluable.

Table 3.

Objective response rate and duration of response by tumour type

	Number of patients per primary diagnosis	Independent review committee assessment		Investigator assessment	
		Objective response rate (95% CI)	Median duration of response, months (IQR)	Objective response rate (95% CI)	Median duration of response, months (IQR)
All *RET* fusion-positive solid tumour types	41	43·9% (28·5–60·3)	24·5 (9·2–NR)	43·9% (28·5–60·3)	18·4 (9·8–22.6)
Pancreatic	11	54·5% (23·4–83·3)	NR (NR–NR)	55·5% (23·4–83·3)	NR (12·0–NR)
Colon	10	20·0% (2·5–55·6)	9·4 (5·6–13·3)	30·0% (6·7–65·3)	9·2 (3·7–9·8)
Salivary	4	50·0% (6·8–93·2)	NR (5·7–NR)	25·0% (0·6–80·6)	5·7 (5·7–5·7)
Unknown primary	3	33·3% (0·8–90·6)	9·2–9·2	33·3% (0·8–90·6)	9·2 (NR–NR)
Breast	2	100·0% (15·8–100·0)	17·3 (17·3–17·3)	100·0% (15·8–100·0)	18·4 (18·4–18·4)
Sarcoma	2	50·0% (1·3–98·7)	14·9 (NR–NR)	50·0% (1·3–98·7)	14·9 (NR–NR)
Xanthogranuloma *	2	NA	NA	50·0% (1·3–98·7)	22·9 (NR–NR)
Carcinoid	1	100·0% (2·5–100·0)	24·1 (NR–NR)	100·0% (2·5–100·0)	18·6 (18·6–18·6)
Ovarian	1	100·0% (2·5–100·0)	14·5 (NR–NR)	100·0% (2·5–100·0)	14·5 (NR–NR)
Small intestine	1	100·0% (2·5–100·0)	24·5 (24·5–24·5)	100·0% (2·5–100·0)	22·6 (22·6–22·6)
Cholangiocarcinoma	1	100·0% (2·5–100·0)	5·6 (NR–NR)	0% (0·0–97·5)	NA
Pulmonary carcinosarcoma	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Rectal neuroendocrine	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Carcinoma of the skin	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA

NA=not applicable. NR=not reached.

* Xanthogranuloma skin cancer could not be evaluated by the independent review committee because of the committee's scope of images not allowing for assessment of skin findings.

Table 4.

Adverse events in *RET* fusion-positive tumour-agnostics safety population (n=45)

	Adverse events, regardless of attribution				Treatment-related adverse events	
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3
Patients with ≥1 adverse event	16 (36%)	22 (49%)	4 (9%)	3 (7%)	23 (51%)	17 (38%)
ALT increased	12 (27%)	7 (16%)	0	0	8 (18%)	7 (16%)
AST increased	11 (24%)	6 (13%)	0	0	8 (18%)	5 (11%)
Dry mouth	15 (33%)	0	0	0	13 (29%)	0
Hypertension	4 (9%)	10 (22%)	0	0	3 (7%)	6 (13%)
Abdominal pain	8 (18%)	4 (9%)	0	0	2 (4%)	0
Diarrhoea	11 (24%)	1 (2%)	0	0	5 (11%)	0
Fatigue	9 (20%)	3 (7%)	0	0	3 (7%)	3 (7%)
Constipation	10 (22%)	0	0	0	4 (9%)	0
Nausea	8 (18%)	2 (4%)	0	0	4 (9%)	0
Blood alkaline phosphatase increased	3 (7%)	4 (9%)	1 (2%)	0	4 (9%)	1 (2%)
Insomnia	8 (18%)	0	0	0	0	0
Pyrexia	8 (18%)	0	0	0	2 (4%)	0
Back pain	7 (16%)	0	0	0	2 (4%)	0
Decreased appetite	7 (16%)	0	0	0	2 (4%)	0
Dyspnoea	6 (13%)	0	0	1 (2%)	2 (4%)	0
ECG QT prolongation	6 (13%)	1 (2%)	0	0	5 (11%)	0
Headache	7 (16%)	0	0	0	1 (2%)	0
Oedema peripheral	7 (16%)	0	0	0	3 (7%)	0
Thrombocytopaenia	7 (16%)	0	0	0	5 (11%)	0
Vomiting	5 (11%)	2 (4%)	0	0	1 (2%)	0
Anaemia	4 (9%)	2 (4%)	0	0	2 (4%)	0
Blood creatinine increased	6 (13%)	0	0	0	3 (7%)	0
Hypokalaemia	5 (11%)	1 (2%)	0	0	1 (2%)	0
Hyponatraemia	2 (4%)	2 (4%)	2 (4%)	0	0	0
Leucopoenia	6 (13%)	0	0	0	4 (9%)	0
Rash	6 (13%)	0	0	0	2 (4%)	0
Weight increased	6 (13%)	0	0	0	2 (4%)	0
Arthralgia	5 (11%)	0	0	0	2 (4%)	0
Blood bilirubin increased	3 (7%)	2 (4%)	0	0	2 (4%)	1 (2%)
Cough	5 (11%)	0	0	0	0	0
Gastroesophageal reflux disease	5 (11%)	0	0	0	2 (4%)	0
Lymphopenia	4 (9%)	1 (2%)	0	0	2 (4%)	0
Pruritus	5 (11%)	0	0	0	1 (2%)	0
Acute kidney injury	1 (2%)	1 (2%)	0	0	NA	NA
Blood lactate dehydrogenase increased	1 (2%)	1 (2%)	0	0	1 (2%)	1 (2%)
Drug-induced liver injury	1 (2%)	1 (2%)	0	0	1 (2%)	1 (2%)

	Adverse events, regardless of attribution				Treatment-related adverse events	
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3
Neutropenia	1 (2%)	2 (4%)	0	0	0	2 (4%)
Proteinuria	2 (4%)	1 (2%)	0	0	1 (2%)	1 (2%)
Chronic kidney disease	0	1 (2%)	0	0	0	1 (2%)
Hypertonia	0	1 (2%)	0	0	0	1 (2%)
Hyperuricaemia	1 (2%)	1 (2%)	0	0	0	1 (2%)
Aspiration	0	0	0	1 (2%)	NA	NA
Neoplasm progression	0	0	0	1 (2%)	NA	NA

Data are n (%). The total percentage for any given adverse event might be different from the sum of the components for the individual grades because of rounding. No patients had grade 4 or 5 treatment-related adverse events. Treatment-emergent adverse events occurring regardless of attribution in 10% or more of patients at grade 1 or 2 in severity, and all grade 3–5 events are shown. Composite terms that are composed of preferred terms are further defined in the appendix (p 10). ALT=alanine aminotransferase. AST=aspartate aminotransferase. ECG=electrocardiogram. NA=not available.