Title Page

CLINICAL STUDY REPORT SYNOPSIS: LOXO-RET-17001

A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET-Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001)

German BfArM (Data Cutoff Date: 30 March 2020)

Approval date provided below.

Approval Date: 06-Oct-2021 GMT

Synopsis

Study Title:

A Phase 1/2 Study of Oral Selpercatinib in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer and Other Tumors with RET Activation (LIBRETTO-001)

Study Number:

LOXO-RET-17001 (Study J2G-OX-JZJA)

Study Phase:

1/2

Compound:

LOXO-292 (selpercatinib); LY3527723

Name of Sponsor/Company:

Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company

Number of Study Centre(s), Participants and Countries:

This study is being conducted at 80 centres that enrolled participants in North America, Asia Pacific, the European Union and the Middle East.

Publications:

Wirth LJ, Sherman E, Robinson B, et al. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. *N Engl J Med.* 2020 ;383(9):825-835.

Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* 2020;383(9):813-824.

Subbiah V, Gainor JF, Oxnard GR, et al. Intracranial Efficacy of Selpercatinib in RET Fusion-Positive Non-Small Cell Lung Cancers on the LIBRETTO-001 Trial. *Clin Cancer Res.* 2021;27(15):4160-4167.

Solomon BJ, Tan L, Lin JJ, et al. RET Solvent Front Mutations Mediate Acquired Resistance to Selective RET Inhibition in RET-Driven Malignancies. *J Thorac Oncol*. 2020;15(4):541-549.

Wirth LJ, Kohno T, Udagawa H, et al. Emergence and Targeting of Acquired and Hereditary Resistance to Multikinase RET Inhibition in Patients With RET-Altered Cancer. *JCO Precis Oncol*. 2019;3(3):PO.19.00189.

Study Period:

Study initiation date: 09 May 2017 (first patient treated)

End date: 30 March 2020 (date of interim data cut-off)

Objectives, Endpoints and Statistical Methods:

The clinical study report (CSR) for LOXO-RET-17001 (Study J2G-OX-JZJA), which was approved on 28 November 2019, includes results from the Phase 1 pharmacokinetic and Phase 2 objective studies as of the data cut-off date of 17 June 2019.

Data from the data cut-off date of 30 March 2020 are reported in this CSR synopsis.

This table lists the objectives and endpoints for the Phase 2 part of the study described in this addendum.

Objectives (Phase 2)	Endpoints (Phase 2)
Primary	
To assess the anti-tumour activity of selpercatinib by determining ORR	ORR based on RECIST 1.1 or RANO, as appropriate to tumour type
Secondary	
To assess the anti-tumour activity of selpercatinib	Parameters of anti-tumour activity/clinical benefit, including: best change in tumour size from baseline, DOR, and CNS ORR and CNS DOR.
To determine the safety profile and tolerability of selpercatinib	Safety per CTCAE (including, but not limited to): frequency and severity of TEAEs, SAEs, deaths and clinical laboratory abnormalities

Abbreviations: CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; IRC = Independent Review Committee; ORR = objective response rate; RANO = Response Assessment in Neuro-Oncology Criteria; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Methodology:

This is a multi-centre, open-label Phase 1/2 study in patients with advanced solid tumours, including rearranged-during-transfection (RET) fusion-positive solid tumours, RET-mutant medullary thyroid cancer (MTC), and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation). This is a single-arm study wherein all patients receive selpercatinib. This study is ongoing and includes 2 parts: Phase 1 (dose escalation) and Phase 2 (dose expansion).

Selpercatinib is administered in oral form once daily (QD) or twice daily (BID), depending upon dose level assignment. Dosing was fixed as a total milligram dose (as opposed to weight-based or body surface area [BSA]-based). A recommended Phase 2 dose (RP2D) of 160 mg BID was selected by the Safety Review Committee (SRC) during Phase 1 of the study. The study is continuing to enrol patients with advanced solid tumours with evidence of a RET gene alteration in tumour and/or blood. Patients are enrolled to 1 of the Phase 2 cohorts based on RET alteration type and prior therapy criteria to better characterise the safety and efficacy of selpercatinib in patients with specific abnormalities in RET. Patients continued selpercatinib dosing in 28-day cycles until disease progression, unacceptable toxicity or other reasons for treatment discontinuation as outlined in Protocol Section 6.4. Four weeks (28 days +7 days) after the last dose of study drug, all treated patients were to undergo a safety follow-up (SFU) assessment.

Number of Participants (Planned and Analysed):

As of the data cut-off date (30 March 2020):

- Participants treated: 746 and
- Participants continuing study: 606.

Enrolment in the study is ongoing.

Diagnosis and Main Criteria for Inclusion and Exclusion:

- Patients with a locally advanced or metastatic solid tumour who progressed on or were intolerant to standard therapy, for whom no standard therapy exists, or, in the opinion of the investigator, were not candidates for, or would be unlikely to tolerate or derive significant clinical benefit from, standard therapy or declined standard therapy.
- For patients being enrolled into a specific Phase 2 dose expansion, evidence of a RET gene alteration in tumour (i.e., not just blood), as defined in Table 4 of the clinical study report (approved on 28 November 2019), was required (a positive germline test for a RET mutation was acceptable for patients with MTC).
- At least 18 years of age. For countries and sites where approved, patients as young as 12 years of age could be enrolled and
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0, 1 or 2 (age ≥16 years) or Lansky Performance Score (LPS) ≥40% (age <16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment.

Duration of Study Intervention:

Individual patients continued selpercatinib dosing until progressive disease (PD), unacceptable toxicity or other reason for treatment discontinuation, as outlined in Protocol Section 6.4. Patients with PD could continue selpercatinib if, in the opinion of the investigator, the patient was deriving clinical benefit from continuing study treatment, and continuation of treatment was approved by the sponsor.

Enrolment, Disposition and Derivations of Analysis Sets

As of the data cut-off date, 30 March 2020, 746 participants were treated in the study. Of the 746 treated patients, 712 patients (95.4%) received at least 1 selpercatinib dose of 160 mg BID. To achieve this:

- 653 patients (87.5%) started at a dose of 160 mg BID,
- 54 patients (7.2%) started at a lower dose and subsequently escalated to 160 mg BID and
- 5 patients (0.7%) dose was reduced to 160 mg BID.

Study intervention was discontinued in 188 patients (25.2%) and 558 patients (74.8%) are continuing study intervention as of the data cut-off date.

The LIBRETTO-001 data are divided into multiple analysis sets as described in the table. Note that patients in the Primary Analysis Set (PAS) are also included in the Integrated Analysis Set (IAS).

Description of Analysis Sets Included in LIBRETTO-001

Analysis Set	Analysis Set Description	Number of Patients
All treated patients (overall safety population): Patients who were enrolled and received at least 1 dose of selpercatinib		**746**
RET fusion-positive NSCLC		345
RET-mutant MTC		315
RET fusion-positive thyroid cancer		42
RET fusion-positive cancers other than thyroid or lung		28
Other cancers[a]		16
Efficacy evaluable population: Patients who have at least 6 months of follow-up from the first dose of selpercatinib at the time of data cut-off.		
***RET* fusion-positive NSCLC**		***302***
IAS	Includes all patients with RET fusion-positive NSCLC previously treated with platinum-based chemotherapy and met the criteria 1-4 in footnote b.	218
PAS	Includes the first 105 consecutively enrolled patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy and met the criteria 1-4 in footnote b. This analysis set is a subset of the "IAS" analysis set.	105
SAS1	Includes treatment-naïve patients with *RET* fusion-positive NSCLC and met Criteria 1, 2 and 4 in footnote b	48
SAS2	Includes patients with *RET* fusion-positive NSCLC previously treated with systemic therapies other than platinum-based chemotherapy and met Criteria 1, 2 and 4 in footnote b	18
SAS3	Includes patients with *RET* fusion-positive NSCLC previously treated and treatment-naive patients without measurable disease by RECIST Version 1.1 and met Criteria 1 and 4 in footnote b	18
***RET*-mutant MTC**		***274***
IAS	Includes all patients with *RET*-mutant MTC enrolled, who received 1 or more lines of prior therapy of cabozantinib or vandetanib and met the Criteria 1, 2, 4 and 5 in footnote b	143
PAS	Includes the first 55 consecutively enrolled patients with *RET*-mutant MTC who received 1 or more lines of prior therapy of cabozantinib or vandetanib and met the Criteria 1, 2, 4 and 5 in footnote b. This analysis set is a subset of the "IAS" analysis set.	55
SAS1	Includes cabozantinib and vandetanib systemic treatment-naive *RET*-mutant MTC patients and met Criteria 1, 2 and 4 in footnote b	112
SAS2	Includes patients with *RET*-mutant MTC previously treated and treatment-naive patients without measurable disease by RECIST Version 1.1 (not included in PAS/IAS/SAS1) and met Criteria 1 and 4 in footnote	19
***RET* fusion-positive thyroid cancer** Includes patients with *RET* fusion-positive thyroid previously treated (N=22) and treatment-naive patients (N=12)		***34***

Abbreviations: CLIA = Clinical Laboratory Improvement Amendments; IAS = Integrated Analysis Set; MTC = medullary thyroid cancer; NSCLC = non-small-cell lung cancer; PAS = Primary Analysis Set; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; RET = rearranged-during-transfection; SAS = Supplemental Analysis Set; US = United Sates.

[a] Other Cancer includes, other RET mutant cancers (non MTC), other RET altered cancers (non-fusion or mutation) and non-RET altered patients.

[b] Criteria for inclusion:

1. Evidence of a protocol-defined qualifying and definitive *RET* fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a *RET* fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included.
2. Measurable disease by RECIST v1.1 by investigator assessment.
3. Received 1 or more lines of prior platinum-based chemotherapy.
4. Received 1 or more doses of selpercatinib.
5. Received 1 or more lines of prior therapy of cabozantinib or vandetanib.

Demography

Almost half of the patients were between 45 and 64 years (354 patients, 47.5%) and were male (386 patients, 51.7%).

Cancer Diagnosis and Baseline Disease Characteristics

The most common cancer types at primary diagnosis in all enrolled participants who received 1 or more doses of selpercatinib were

- *RET* fusion-positive NSCLC (345 patients, 46.2%),
- *RET*-mutant MTC (315 patients, 42.2%),
- *RET* fusion-positive thyroid cancer (42 patients, 5.6%),
- *RET* fusion-positive other than thyroid or lung (28 patients, 3.8%) and
- Other tumours (16 patients, 2.1%).

More than half of the patients had ECOG PS of 1 (436 patients, 58.4%) at baseline. Baseline ECOG PS of 2 was reported for 35 patients (4.7%).

Exposure

At the time of the data cut-off date (30 March 2020), 746 patients received at least 1 dose of selpercatinib. Most patients (653, 87.5%) received the RP2D of 160 mg BID as a starting dose. The median time on treatment was 11.07 months (min, max: 0.0, 34.5).

Efficacy Results:

The efficacy of selpercatinib in the following patient populations is presented:

- *RET* fusion-positive NSCLC patients who received 1 or more lines of prior platinum-based chemotherapy (PAS and IAS),
- *RET*-mutant MTC patients who received 1 or more lines of prior therapy of cabozantinib or vandetanib (PAS and IAS) and
- *RET* fusion-positive thyroid cancer patients who received at least 1 prior systemic therapy other than Radioactive iodine (RAI).

***RET* Fusion-Positive NSCLC**

Efficacy in patients previously treated with platinum-based chemotherapy:

- In the PAS (N = 105), a clinically meaningful 63.8% objective response rate (ORR) by an Independent Review Committee (IRC) was observed (95% confidence interval [CI]: 53.9, 73.0).
- Median duration of response (DOR) by an IRC was 17.5 months (95% CI: 12.1, not evaluable [NE]), with a median follow-up of 15.7 months.
- The ORR results by an IRC (56.9%, 95% CI: 50.0, 63.6) from the larger IAS of patients (N = 218) with the same inclusion criteria as the PAS were consistent with those of the PAS and
- Among the RET fusion-positive NSCLC patients (IAS), 96 had central nervous system (CNS) metastasis according to IRC, including 23 patients with measurable CNS lesions according to an IRC assessment. The ORR in the evaluable measurable CNS patients was 87% (20/23; 95% CI: 66.4, 97.2) and the DOR was 9.36 months (range: 2.8 to 23.9+).

***RET*-Mutant Medullary Thyroid Cancer**

Efficacy in patients previously treated with cabozantinib and/or vandetanib:

- In the PAS (N = 55), clinically meaningful ORR by an IRC of 69.1% was observed (95% CI: 55.2, 80.9).
- Median DOR in the PAS was not reached, with a median follow-up of 17.45 months and
- The ORR by an IRC of 69.2% (95% CI: 61.0, 76.7) observed in the larger population of patients (IAS, n = 143) is comparable and supports the results of the PAS.

***RET* Fusion-Positive Thyroid Cancer**

Efficacy in patients with previously treated *RET* fusion-positive patients:

- For the 22 previously treated patients with *RET* fusion-positive thyroid cancer, a clinically meaningful ORR by an IRC of 77.3% (95% CI: 54.6, 92.2) was observed and
- The median DOR was 18.4 months (95% CI: 10.1, NE), with a median follow-up of 20.3 months.

The key efficacy results for *RET* fusion-positive NSCLC, *RET*-mutant MTC and *RET* fusion-positive thyroid cancer are presented in the Table 1.

Table 1. Objective Response and Duration of Response for RET Fusion-Positive NSCLC, RET-Mutant Medullary Thyroid Cancer and RET Fusion-Positive Thyroid Cancer

	Primary Analysis Set (PAS) IRC Assessment	**Efficacy Eligible Patients (IAS) IRC Assessment**
***RET* fusion-positive NSCLC patients previously treated with platinum-based chemotherapy**		
n	105	218
Objective response (CR + PR)		
Percentage (%)	63.8	56.9
95% CI	(53.9, 73.0)	(50.0, 63.6)
CR, n (%)	3 (2.9)	9 (4.1)
PR, n (%)	64 (61.0)	115 (52.8)
Duration of response (months)		
Median	17.5	17.5
95% CI	12.1, NE	12.1, NE
Response status		
Censored, n (%)	39 (58.2)	86 (69.4)
Median duration of follow-up, months	15.67	11.99
25th, 75th percentiles	12.1, 18.2	7.4, 15.9
***RET*-mutant MTC patients previously treated with cabozantinib and/or vandetanib**		
n	55	143
Objective response (CR + PR)		
Percentage (%)	69.1	69.2
95% CI	(55.2, 80.9)	(61.0, 76.7)
CR n (%)	6 (10.9)	6 (4.2)
PR n (%)	32 (58.2)	93 (65.0)
Duration of response (months)		
Median	NE	NE
95% CI	(19.1, NE)	(19.1, NE)
Response Status		
Censored, n (%)	29 (76.3)	81 (81.8)
Median duration of follow-up (months)	17.45	10.05
25th, 75th Percentiles	12.9, 22.0	5.9, 15.9
Previously treated *RET* fusion-positive thyroid cancer patients		
	Efficacy eligible patients IRC assessment	
n	22	
Objective response (CR + PR)		
Percentage (%)	77.3	
95% CI	54.6, 92.2	
CR n (%)	2 (9.1)	
PR n (%)	15 (68.2)	
Duration of response (months)		
Median	18.4	
95% CI	10.1, NE	

	Primary Analysis Set (PAS) IRC Assessment	Efficacy Eligible Patients (IAS) IRC Assessment
Response status		
Censored, n (%)	9 (52.9)	
Median duration of follow-up (months)	20.27	
25th, 75th Percentiles	12.6, 25.4	

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; MTC = medullary thyroid cancer; n = number of participants in the specified category; NE = not evaluable; NSCLC = non-small-cell lung cancer; PR = partial response; RET = rearranged-during-transfection.
Data cut-off date: 30 March 2020.

Safety Results:

Treatment-Emergent Adverse Events

Most patients (99.2%) experienced at least 1 treatment-emergent adverse event (TEAE) during treatment.

The most common TEAEs, defined as those reported in at least 20% patients, were:

- dry mouth (40.2%),
- diarrhoea (38.7%),
- hypertension (36.6%),
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased (32.6%),
- fatigue (31.2%),
- constipation (27.1%),
- oedema peripheral (25.7%),
- headache (23.6%),
- nausea (23.5%) and
- blood creatinine increased (20.6%).

Grade ≥3 TEAEs

Grade ≥3 TEAEs were reported in 470 (63%) patients. The most common Grade ≥3 events were hypertension (19.2%), ALT increase (9.8%) and AST increase (8.3%).

Table 2 presents TEAEs reported in ≥20% of patients and the corresponding events of Grade ≥3 severity by relatedness to study drug.

Serious Adverse Events

A total of 262 (35.1%) of the 746 patients experienced a treatment-emergent serious adverse event (SAE). The most frequently reported serious TEAEs (reported by ≥1% of total patients) were

- pneumonia (3.1%)
- dyspnoea and hyponatraemia (1.9% each)
- ALT and AST increased (1.6% each)
- abdominal pain (1.5%)
- pleural effusion (1.5%)
- drug hypersensitivity (1.3%)
- diarrhoea (1.2%)
- acute kidney injury and pyrexia (1.1% each)

Serious TEAEs considered related (assessed by the investigator) to study intervention were reported by 62 patients (8.3%). The most frequently reported serious TEAEs related to study intervention (reported by ≥1% of total patients) were drug hypersensitivity (1.3%) and ALT and AST increased (1.2% each).

Serious TEAEs with fatal outcomes were reported in 25 patients (3.4%), all of which were considered unrelated to study intervention.

Table 3 provides details of SAEs and related SAEs.

Deaths

Overall, 104 patients died as of the 30 March 2020 data cut-off. One hundred and three (13.8%) patient deaths were deemed as on-study deaths, because they occurred within 28 days of the last dose of study drug: disease progression (70 patients), adverse events (AEs; 25 patients) and other/unknown (8 patients).

No deaths were considered related to selpercatinib. No pattern was noted in AEs leading to death; cardiac arrest and sepsis were reported in 3 patients each (0.4%), with all other fatal AEs reported in 1 or 2 patients each.

Adverse Events Leading to Treatment Discontinuation or Dose Modification

Forty-five patients (6.0%) permanently discontinued treatment because of an AE, with no predominant pattern among the specific AEs reported or any new safety concerns: 16 of the 45 patients (2.1% of all patients treated) discontinued selpercatinib because of a treatment-related AE.

Nine AEs led to treatment discontinuation in more than 1 patient:

- ALT increased and sepsis (3 patients each, 0.4%) and
- AST increased, cardiac failure, drug hypersensitivity, fatigue, pericardial effusion, pneumonia and thrombocytopenia (2 patients each, 0.3%).

Table 4 provides TEAEs reported as the reason for study drug discontinuation by more than 1 patients.

Two hundred and fifty-one (33.6%) patients had dose reductions due to any AE. The most common TEAEs that led to dose reductions were

- ALT increase (53 patients, 7.1%),
- AST increase (48 patients, 6.4%),
- fatigue (20 patients, 2.7%),
- QT prolongation (19 patients, 2.5%) and
- drug hypersensitivity (17 patients, 2.3%).

Three hundred and thirty-four (44.8%) patients had dose interruptions due to any AE. The most common TEAEs that led to dose interruptions were

- ALT increase (42 patients, 5.6%),
- AST increase and hypertension (each in 37 patients, 5.0%),
- diarrhoea (24 patients, 3.2%),
- pyrexia (20 patients, 2.7%) and
- electrocardiogram (ECG) QT prolongation (16 patients, 2.1%).

Table 5 provides TEAEs reported as the reason for study drug reduced, and study drug interrupted by more than or equal to 2 patients.

Adverse Events of Special Interest

Three adverse events of special interest (AESI) identified early in the clinical program were ALT or AST increased, drug hypersensitivity and hypertension. All of these AEs are monitorable and are reversible with dose interruptions, reductions or discontinuations.

AST/ALT Increased
Aspartate aminotransferase increases were observed in 243 (32.6%) patients. Grade ≥3 ALT and AST elevations occurred in 73 (9.8%) and 62 (8.3%) patients respectively. Frequent monitoring of liver function tests, together with the implementation of a dose-modification strategy when the elevations occurred, allowed most patients with AST/ALT increases to experience normalised AST/ALT and continue selpercatinib. Permanent discontinuation of study drug due to AST/ALT increases occurred for 5 patients. Dose modification details for the patients with increases in ALT or AST were

- ALT increased: 42 (5.6%) patients had dose interruption and 53 (7.1%) patients had dose reduction and
- AST increased: 37 (5.0%) patients had dose interruption and 48 (6.4%) patients had dose reduction.

Hypersensitivity
Hypersensitivity was analysed as a composite term including the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) of 'hypersensitivity' and 'drug hypersensitivity.'

Hypersensitivity was noted in 39 (5.2%) patients, most of these events were observed in NSCLC patients (n=31).

Of the 39 patients,

- 13 (1.7%) patients experienced ≥ Grade 3 events,
- 31 (4.2%) patients had hypersensitivity related to study drug,
- 14 (1.9%) patients had SAEs of hypersensitivity, all of which were related to the study drug and
- 26 patients (3.5%) underwent dose reduction, 6 patients (0.8%) underwent dose interruption and 3 patients (0.4%) had study-drug discontinuation as the most significant action taken.

Hypertension
The composite term of Hypertension was analysed using MedDRA PTs 'hypertension', 'blood pressure increased' and 'blood pressure abnormal' for overall incidence.

Hypertension (composite term) was reported in 279 patients (37.4%), of whom

- 145 (19.4%) patients had Grade ≥3 hypertension,
- Hypertension (PT) and blood pressure increased (PT) were considered related to study drug in 190 (25.5%) and 7 (0.9%) patients respectively,
- 37 (5.0%) patients had dose interruption and 10 (1.3%) patients had a dose reduction due to hypertension (PT) and
- 1 of 746 (0.1%) patients had a dose interruption due to blood pressure increased (PT), and none had a dose reduction. One patient discontinued from the study due to hypertension (PT).

Other Notable Event: Electrocardiogram QT Prolongation

Electrocardiogram QT prolonged was a notable AE that was reported in 135 (18.1%) patients, of which

- 30 (4.0%) patients had events ≥Grade 3,
- no torsades de pointes were reported**,**
- no patient discontinued treatment due to QT prolongation and
- 16 (2.1%) patients had dose interruption and 19 (2.5%) patients had dose reduction due to QT prolongation.

Table 6 provides details of AESIs and notable events.

Clinical Laboratory Evaluation

Laboratory evaluations did not reveal major trends, aside from the observed elevations in AST and ALT, that were mostly Grade 1 and Grade 2 and were reversible. The most common (reported ≥5% of patients) Grade 3/4 treatment-emergent laboratory abnormalities were

- lymphocyte count decreased (114 patients [16.1%]),
- ALT elevations (78 patients [10.6%]),
- AST elevations (66 patients [9.0%]) and
- sodium decreased (63 patients [8.5%]).

Table 7 provides a summary of the treatment-emergent abnormal laboratory values.

Table 2. Overall Incidence of TEAEs in ≥20% of Patients in Decreasing Order of Frequency Safety Population

	All Patients (N = 746)			
MedDRA Preferred Term	**TEAEs Any Grade**	**Drug-Related TEAEs Any Grade**	**TEAEs of Severity Grade ≥3**	**Drug-Related TEAEs of Severity Grade ≥3**
Patients with any TEAEs, n (%)	**740 (99.2)**	**690 (92.5)**	**470 (63.0)**	**239 (32.0)**
Dry mouth	300 (40.2)	265 (35.5)	0 (0.0)	0 (0.0)
Diarrhoea	289 (38.7)	163 (21.8)	26 (3.5)	12 (1.6)
Hypertension	273 (36.6)	190 (25.5)	143 (19.2)	93 (12.5)
Aspartate aminotransferase increased	243 (32.6)	196 (26.3)	62 (8.3)	47 (6.3)
Alanine aminotransferase increased	243 (32.6)	197 (26.4)	73 (9.8)	60 (8.0)
Fatigue	233 (31.2)	144 (19.3)	11 (1.5)	8 (1.1)
Constipation	202 (27.1)	97 (13.0)	4 (0.5)	2 (0.3)
Oedema peripheral	192 (25.7)	108 (14.5)	2 (0.3)	0 (0.0)
Headache	176 (23.6)	65 (8.7)	11 (1.5)	3 (0.4)
Nausea	175 (23.5)	75 (10.1)	5 (0.7)	2 (0.3)
Blood creatinine increased	154 (20.6)	88 (11.8)	1 (0.1)	0 (0.0)

- Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients treated; n = number of patients in specific category; TEAE = treatment-emergent adverse event.
- Notes: Percentage is calculated using the number of patients in the column heading as the denominator. TEAEs are defined as adverse events that started on or after the first administration of study drug. Patients are counted once within each preferred term. Patients with multiple severity ratings for a given AE are counted once under the maximum severity. Related events are those judged by the investigator as related to the study drug. Severity grade assignment based on CTCAE version 4.03: Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal). Reported AE terms were coded using MedDRA version 21.0.

Table 3. Overall Incidence of SAEs in ≥1% of Patients in Decreasing Order of Frequency Safety Population

MedDRA Preferred Term	All Patients (N = 746)	
	Total Patient Incidence of Treatment-Emergent SAEs by Frequency (≥1% patients)	Total Patient Incidence of Treatment-Related Treatment-Emergent SAEs
Patients with any SAEs n (%)	**262 (35.1)**	**62 (8.3)**
Pneumonia	23 (3.1)	0
Dyspnoea	14 (1.9)	0
Hyponatraemia	14 (1.9)	0
Alanine aminotransferase increased	12 (1.6)	9 (1.2)
Aspartate aminotransferase increased	12 (1.6)	9 (1.2)
Abdominal pain	11 (1.5)	2 (0.3)
Pleural effusion	11 (1.5)	0
Drug hypersensitivity	10 (1.3)	10 (1.3)
Diarrhoea	9 (1.2)	3 (0.4)
Acute kidney injury	8 (1.1)	0
Pyrexia	8 (1.1)	2 (0.3)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients treated; n = number of patients in specific category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Notes: Percentage is calculated using the number of patients in the column heading as the denominator. TEAEs are defined as AEs that started on or after the first administration of study drug. Patients are counted once within each preferred term. Reported AE terms were coded using MedDRA Version 21.0.

Table 4. Treatment-Emergent Adverse Events Reported as Reason for Study Treatment Discontinuation Safety Population

MedDRA Preferred Term	All Patients (N = 746)
	TEAEs of Any Grade n (%)
Patients with TEAEs with study drug permanently discontinued	**45 (6.0)**
TEAEs leading to discontinuation in more than 1 patient	
ALT increased	3 (0.4)
Sepsis	3 (0.4)
AST increased	2 (0.3)
Cardiac failure	2 (0.3)
Drug hypersensitivity	2 (0.3)
Fatigue	2 (0.3)
Pericardial effusion	2 (0.3)
Pneumonia	2 (0.3)
Thrombocytopenia	2 (0.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of patients in the safety population; n = number of patients within category; TEAE = treatment-emergent adverse event.

Table 5. Treatment-Emergent Adverse Events Reported as Reason for Study Drug Reduced and Study Drug Interrupted
Safety Population

MedDRA Preferred Term	All Patients (N = 746) n (%)
Patients with TEAEs with Dosage Reduced	**251 (33.6)**
Most common (≥2%) TEAEs leading to dose reduction	
ALT increased	53 (7.1)
AST increased	48 (6.4)
Fatigue	20 (2.7)
Electrocardiogram QT prolonged	19 (2.5)
Drug hypersensitivity	17 (2.3)
Patients with TEAEs with Study Drug Interrupted	**334 (44.8)**
Most common (≥2%) TEAEs leading to dose interruption	
ALT increased	42 (5.6)
AST increased	37 (5.0)
Hypertension	37 (5.0)
Diarrhoea	24 (3.2)
Pyrexia	20 (2.7)
Electrocardiogram QT prolonged	16 (2.1)

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of patients in the safety population; n = number of patients within category; TEAE = treatment-emergent adverse event.

Table 6. Overall Incidence of AESIs and Notable event
Safety Population

MedDRA Preferred Term	All Patients (N = 746)	
	TEAEs of Any Grade n (%)	TEAEs of Severity Grade ≥3 n (%)
AESI		
ALT Increase	243 (32.6)	73 (9.8)
AST Increase	243 (32.6)	62 (8.3)
Hypersensitivity	39 (5.2)	13 (1.7)
Hypertension	279 (37.4)	145 (19.4)
Other Notable Event		
Electrocardiogram QT Prolongation	135 (18.1)	30 (4.0)

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of patients in the safety population; n = number of patients within category; TEAE = treatment-emergent adverse event.

Table 7. Summary of Incidence of Treatment-Emergent Abnormal Laboratory Tests, Reported in Greater ≥20% of the Total Population, Safety Population

Laboratory Test	Total (N = 746)		
	N1	Grade 3-4 n (%)	All Grades n (%)
Aspartate aminotransferase increased	737	66 (9.0)	405 (55.0)
Alanine aminotransferase increased	737	78 (10.6)	365 (49.5)
Lymphocyte count decreased	710	114 (16.1)	328 (46.2)
Glucose increased	737	14 (1.9)	336 (45.6)
Calcium decreased	737	30 (4.1)	335 (45.5)
Albumin decreased	736	10 (1.4)	331 (45.0)
WBC count decreased	737	14 (1.9)	324 (44.0)
Creatinine increase[a]	737	9 (1.2)	288 (39.1)
Alkaline phosphatase increased	737	19 (2.6)	271 (36.8)
Platelets decreased	737	22 (3.0)	254 (34.5)
Sodium decreased	737	63 (8.5)	226 (30.7)
Total cholesterol increased	722	1 (0.1)	222 (30.7)
Potassium increased	737	11 (1.5)	195 (26.5)
Glucose decreased	737	6 (0.8)	193 (26.2)
Magnesium decreased	734	4 (0.5)	188 (25.6)
Total bilirubin increased	737	16 (2.2)	181 (24.6)
Neutrophil count decreased	715	22 (3.1)	152 (21.3)
Haemoglobin decreased	737	14 (1.9)	152 (20.6)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MTC = medullary thyroid cancer; n = number of participants in the specified category; N1 = number of patients with at least a baseline result and 1 postbaseline result, used as denominators for the percentages; NSCLC = non-small-cell lung cancer; RET = rearranged-during-transfection; WBC = white blood cell.

Note: Percentage is calculated based on the number of patients in the corresponding safety analysis set (N) with baseline assessment and at least one post-baseline assessment as the denominator (n').

The worst post-baseline severity grade is used for every subject.

Toxicity grade assignment based on CTCAE (Version 4.03).

[a] Toxicity grade assignment based on CTCAE (Version 5.0).

Treatment-emergent post-baseline grade is a grade that is worse than baseline grade for a given parameter in either direction of increase or decrease.

Conclusions:

As of the data cut-off date, 746 participants with advanced solid tumours have been treated. Cancer types include *RET* fusion-positive NSCLC (46.2%), *RET*-mutant MTC (42.2%), *RET* fusion-positive other tumours (3.8%) and Other tumours (2.1%).

Based on IRC assessments, the ORR was 63.8% (95% CI: 53.9, 73) in *RET* fusion-positive NSCLC patients previously treated with platinum-based chemotherapy, 69.1% (95% CI: 55.2, 80.9) in *RET*-mutant MTC patients previously treated with cabozantinib and/or vandetanib and 77.3% (95% CI: 54.6, 92.2) in previously treated *RET* fusion-positive thyroid cancer patients.

The vast majority of patients (87.5%) received the proposed starting dose of selpercatinib 160 mg BID, suggesting that the safety experience to date reflects the expected real-world use.

The AE profile of selpercatinib was manageable, with low rate of treatment discontinuations due to an AE (6.0%). When dose interruptions due to AEs (44.8%) or reductions due to AEs (33.6%) occurred, most patients recovered and continued treatment.

Selpercatinib was well tolerated across all tumour types studied, with a safety profile characterised by recognisable toxicities, which can be monitored, with dose interruption or addressed through dose reduction or concomitant medication.

In summary, the results from this study indicate that selpercatinib leads to clinically meaningful, durable responses in patients with RET fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy and RET-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib and RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or Lenvatinib.

Ergänzende Angaben zur Synopse

1. Sponsor der Studie

Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company
281 Tresser Boulevard, 9th Floor
Stamford CT 06901, USA

2. Name des Endproduktes:

Retsevmo®

3. Name des Wirkstoffs:

Selpercatinib

6. Prüfärzte + 7. Namen und Adressen aller Studienzentren

Investigator Name	Site Contact Information
Drilon, Alexander	David H. Koch Center for Cancer Care at Memorial Sloan Kettering Cancer Center 1275 York Ave, New York, NY 10065, United States
Bauer, Todd	Sarah Cannon and HCA Research Institute 250 25th Avenue North Suite 307, Nashville, TN 37203, United States
Subbiah, Vivek	MD Anderson Cancer Center 1515 Holcombe Blvd Unit 455, Houston, TX 77030, United States
Bazhenova, Lyudmila	University of California, San Diego (UCSD) - Medical Center Moores Cancer Center Clinical Trials Office 3855 Health Sciences Drive Room 2014, La Jolla, CA 92093-0698, United States
Shah, Manisha	The Ohio State University (OSU) A438 Starling-Loving Hall 320 West 10th Avenue, Columbus, OH 43210, United States
McCoach, Caroline	University of California, San Francisco (UCSF) - Helen Diller Family Comprehensive Cancer Center 1600 Divisadero St. San Francisco, CA 94115, United States
Lakhani, Nehal	South Texas Accelerated Research Therapeutics (START) Midwest 5800 Foremost Drive SE Suite 100, Grand Rapids, MI 49546, United States
Pennell, Nathan	Cleveland Clinic 9500 Euclid Ave, Rb-35, Cleveland, OH 44195, United States
Wirth, Lori	Massachusetts General Hospital 55 Fruit Street, Boston, MA 02114, United States
Bestvina, Christine	University of Chicago 5841 S. Maryland Ave. MC6091, Chicago, IL 60637, United States
Lorch, Jochen	Dana-Farber Cancer Institute 450 Brookline Ave, Boston, MA 02215, United States
Massarelli, Erminia	City of Hope National Medical Center 1500 E Duarte Road, Duarte, CA 91010, United States
Falchook, Gerald	Sarah Cannon Research Institute at HealthONE 1800 Williams St ; #300, Denver, CO 80218, United States

Goldman, Jonathan	University of California, Los Angeles (UCLA) - Medical Center, UCLA Hematology-Oncology, 10945 LeConte Avnenue Suite 3660, Los Angeles, CA 90095, United States
Weiss, Jared	University of North Carolina (UNC) - Chapel Hill, 450 W. Drive Campus Box 7295, Chapel Hill, NC 27599, United States
Levy, Benjamin	Johns Hopkins Kimmel Cancer Center 5255 Loughboro Rd, Washington, DC 20016, United States
Worden, Francis	University of Michigan 1500 E. Medical Center Dr., Ann Arbor, MI 48109, United States
Akerley, Wallace	Huntsman Cancer Institute 2000 Circle of Hope, Salt Lake City, UT 84112, United States
Vuky, Jacqueline	Oregon Health & Science University (OHSU) 3181 SW Sam Jackson Park Road, Portland, OR 97239, United States
Owonikoko, Taofeek	Emory University School of Medicine 1365-C Clifton Road NE Suite C3012, Atlanta, GA 30322, United States
Berlin, Jordan	Vanderbilt University School of Medicine 2220 Pierce Avenue, 777 Preston Research Building, Nashville, TN 37232, United States
Spira, Alexander	Virginia Cancer Specialists Fairfax Office 8503 Arlington Blvd. Suite 400, Fairfax, VA 22031, United States
Matrana, Marc	Ochsner Clinic Foundation 1514 Jefferson Highway, New Orleans, LA 70121, United States
Morris, John	Mayo Clinic – Rochester 200 First Street, SW, Rochester, MN 55905, United States
Raez, Luis	Memorial Hospital 801 N Flamingo Road, Ste 11, Pembroke, FL 33028, United States
Burkard, Mark	University of Wisconsin - Carbone Cancer Center 600 Highland Avenue, Madison, WI 53792, United States
Zhu, Viola	University of California - Irvine Medical Center 101 City Drive South, Building 56, Suite 500, Orange, CA 92868, United States
Waqar, Saiama	Washington University School of Medicine 660 S. Euclid Ave. Campus Box 8011, St. Louis, MO 63110, United States
Brose, Marcia	University of Pennsylvania 422 Curie Boulevard, PA Room M8, Philadelphia, PA 19104, United States
Wilson, Frederick	Yale University School of Medicine – Yale Cancer Center 15 York Street, WWW224, New Haven, CT 06510, United States
Agosto Salgado, Sarimar	University of Texas Southwestern 5323 Harry Hines Blvd, Dallas, TX 75390, United States
Dy, Grace	Roswell Park Comprehensive Cancer Center Elm and Carlton Streets, Buffalo, NY 14263, United States
Rolfo, Christian	University of Maryland Medical Center 22 Greene Street, Room N3W77, Baltimore, MD 21201, United States
Braiteh, Fadi	Comprehensive Cancer Centers of Nevada 3730 S. Eastern Ave. Las Vegas, NV 89169, United States
Velcheti, Vamsidhar	New York University (NYU) Langone Medical Center 522 First Avenue, New York, NY 10016, United States
Karlin, Nina	Mayo Clinic – Scottsdale 13400 East Shea Blvd, Scottsdale, AZ 85259, United States
Bernet, Victor	Mayo Clinic – Jacksonville 4500 San Pablo Road South Mayo Clinic, Division Endocrinology, Jacksonville, FL 32224, United States
Pan, Ming-Gui	Kaiser Permanente - Santa Clara, CA 710 Lawrence Expressway, Santa Clara, CA 95051, United States
Suga, Jennifer	Kaiser Permanente- Vallejo, Kaiser Permanente Medical Center 975 Sereno Drive, Vallejo, CA 94589, United States
Park, Keunchil	Samsung Medical Center 81 Irwon-ro, Gangnam-gu, Seoul, 06351, South Korea
Han, Ji-Youn	National Cancer Center 323 Ilsan-ro, Ilsandong-gu, Goyang-si Gyeonggi-do, 10408, South Korea

Kim, Yu Jung	Seoul National University Bundang Hospital 82, Gumi-ro 173, Beon-Gil, Bundang-gu, Seongnam-si, Gyeonggi-do, 13620, South Korea
Cho, Byoung Chul	Severance Hospital, Yonsei University Health System 50-1, Yonsei-ro, Seodaemun-gu, Seoul, 03722, South Korea
Lee, Dae Ho	Asan Medical Center 88, Olympic-ro, 43-gil, Songpa-gu, Seoul, 05505, South Korea
Yang, James Chih-Hsin	National Taiwan University Hospital 7, Chung-Shan S. Rd., Zhongzheng District, Taipei City, 10002 R.O.C, Taiwan
Hsu, Kuo-Hsuan (Jun 2020 – present)	Taichung Veterans General Hospital No. 1650 Taiwan Boulevard, Section 4, Taichung, 40705, Taiwan
Loong, Herbert Ho Fung	Prince of Wales Hospital 30-32 Ngan Shing Street, Shatin, Hong Kong
Laskin, Janessa	British Columbia Cancer Agency Vancouver Cancer Center, 600 West 10th Ave Vancouver, British Columbia V5z 4E6, Canada
Peled, Nir	Soroka University Medical Center Dept. of Oncology,Rager Blvd. Beer-Sheva, 8410101, Israel
Golan, Talia	Sheba Medical Center Derech Sheba 2, Tel Hashomer, 5265601, Israel
Nechushtan, Hovav	Hadassah Medical Center Ein Karem Hadassah Medical Center - Clinical Trials Unit, Research Fund of the Hadassah Medical Organization Kiryat Hadassah, Jerusalem, 9112001, Israel
Goto, Koichi	National Cancer Center Hospital East 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan
Ohe, Yuichiro	National Cancer Center Hospital 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan
Nishio, Makoto	Cancer Institute Hospital of JFCR 3-8-31, Ariake, Koto, Tokyo, 135-8550, Japan
Kenmotsu, Hirotsugu	Shizuoka Cancer Center 1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777, Japan
Daga, Haruko	Osaka City General Hospital 2-13-22 Miyakojima-hondori, Miyakojima-ku, Osaka, Osaka, 5340021, Japan
Satouchi, Miyako	Hyogo Cancer Center 13-70, Kitaouji-cho, Akashi, Hyogo, 673-8558, Japan
Toyozawa, Ryo	National Hospital Organization Kyushu Cancer Center 3-1-1 Notame, Minami-ku, Fukuoka, Fukuoka, 811-1347, Japan
Morise, Masahiro	Nagoya City University Hospital 65 Tsurumai-cho, Showa-ku, Nagoya-city, Aichi, Nagoya, 466-8560, Japan
Takeuchi, Shinji	Kanazawa University Hospital 13-1 Takara-machi, Kanazawa, Ishikawa, 920-8641, Japan
Takeda, Masayuki	Kindai University Hospital 377-2, Ohno-higashi, Osaka-sayama, Osaka, 589-8511, Japan
Sakamoto, Tomohiro	Tottori University Hospital 36-1 Nishi-cho, Yonago, Tottori, 683-8504, Japan
Ohashi, Kadoaki	Okayama University Hospital 2-5-1 Shikata-cho, Kita-ku, Okayama, Okayama, 700-8558, Japan
Sakakibara, Jun	Hokkaido University Hospital Kita 14, Nishi 5, Kita-ku, Sapporo, Hokkaido, 060-8648, Japan
Tan, Shao Weng Daniel	National Cancer Centre Singapore Clinical Trials Office, CTE, Level 4, 11 Hospital Drive, Singapore, 169610, Singapore
Solomon, Benjamin	Peter MacCallum Cancer Institute 305 Grattan Street, Melbourne, 3000, Australia
Robinson, Bruce	Royal North Shore Hospital Level 7, Kolling Building, Royal North Shore Hospital, St Leonards, NSW 2065, Australia
Besse, Benjamin	Gustave Roussy, 114 rue Edouard Vaillant, VILLEJUIF, 94805, France

Italiano, Antoine	Institut Bergonie 229, cours de l'Argonne, Bordeaux Cedex, 33076, France
Tomasini, Pascale	AP-HM - Hôpital de la Timone CEPCM, 264 rue St. Pierre, Marseille, 13005, France
Cassier, Philippe	Centre Leon Berard 28, rue Laennec, Lyon, 69008, France
Medioni, Jacques	Hôpital Européen Georges Pompidou - AP-HP Service de cancérologie médicale, Bureaux de recherche clinique 4ème C, 20 rue Leblanc, Paris, 75015, France
de Braud, Filippo	Fondazione IRCCS Istituto Nazionale dei Tumori Via Giacomo Venezian, 1, Struttura Complessa Oncologia Medica I, Milano, 20133, Italy
Boni, Valentina	Centro Integral Oncologico Clara Campal START Madrid, Unidad Ensayos Clinicos Fase I_Planta 3, Hospital HM Universitario Sanchinarro, Calle Oña nº 10, Madrid, 28050, Spain
Moreno Garcia, Victor	Fundacion Jimenez Diaz START-Madrid-FJD, Avda Reyes Catolicos 2nd Floor 1, Madrid, 28040, Spain
Garralda Cabanas, Elena	Hospital Universitario Vall d'Hebron Passeig de la Vall d'Hebron 119-129, Barcelona, 08035, Spain
Minchom, Anna	Royal Marsden Hospital – Surrey Haemato-Oncology Department, Sycamore House Downs Road Sutton, Surrey, SM2 5PT, United Kingdom
Wolf, Jürgen	Universitaetsklinikum Koeln (AoeR) Kerpener Str. 62, Innere Medizin I - Klinische Infektiologie, Koeln, 50937, Germany
Kroiss, Matthias	Universitaetsklinikum Wuerzburg Josef-Schneider-Str. 2, Wuerzburg, 97080, Germany
Staal Rohrberg, Kristoffer	Rigshospitalet Blegdamsvej 9, Copenhagen, 2100, Denmark
Gautschi, Oliver	Luzerner Kantonsspital 6000 Luzern 16, Luzern, 6000, Switzerland

15. Batch-Nummern

Drug Product Lot	**Description**
17-0076	20 mg capsules, simple blend
17-0077	80 mg capsules, simple blend
17-0126	20 mg capsules, simple blend
17-0127	80 mg capsules, simple blend
18-0012-A	80 mg capsules, simple blend
18-0012-B	80 mg capsules, simple blend
1808232-A	80 mg capsules, simple blend
1901011-B	40 mg capsules, simple blend
1901012-B	80 mg capsules, simple blend
DP-APS17-112-A	20 mg capsules, neat
DP-APS17-125-A	10 mg capsules, simple blend
DP-APS17-171-A	20 mg capsules, simple blend
DP-APS17-172-A	80 mg capsules, simple blend
DP-APS18-116-A	20 mg capsules, simple blend
DP-APS18-117-A	80 mg capsules, simple blend
DP-APS18-123-A	80 mg capsules, simple blend
DP-APS18-139-A	80 mg capsules, simple blend
DP-APS18-140-A	80 mg capsules, simple blend

DP-APS18-154-A	20 mg capsules, simple blend
DP-APS18-162-A	80 mg capsules, simple blend
DP-APS19-108-A	20 mg capsules, simple blend
DP-APS18-126	Powder for oral suspension, 5g
DP-APS18-155	Powder for oral suspension, 5g
DP-APS18-174	Powder for oral suspension, 5g
DP-APS19-163	Powder for oral suspension, 5g
1902054-B	80 mg capsules, simple blend
DP-APS19-162-A	20 mg capsules, simple blend
1902053-B	40 mg capsules, simple blend
1907208-A	40 mg capsules, simple blend
1907209-A	40 mg capsules, simple blend
1907210-A	40 mg capsules, simple blend
1907203-A	80 mg capsules, simple blend
1907204-A	80 mg capsules, simple blend
1907205-A	80 mg capsules, simple blend
1907206-A	80 mg capsules, simple blend
2001018-A	40 mg capsules, simple blend

21. Date of report

Approval: 06.10.2021
Ergänzende Angaben: 08.10.2021