Treatment patterns and outcomes of RET fusion-positive non-small-cell lung cancer (NSCLC) patients treated with selpercatinib in Europe: Interim Results from the SPRINT-RET study.

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OBJECTIVE

- To describe the characteristics, treatment patterns, and outcomes for patients with rearranged during transfection (*RET*) fusion-positive non-small-cell lung cancer (NSCLC) treated with selpercatinib from the interim data cut of the SPRINT-RET study.

CONCLUSION

- The rwORR and median rwPFS demonstrated strong real-world effectiveness of selpercatinib, comparable to the Phase 3 LIBRETTO-431 trial interim analysis and long-term follow-up of the Phase 1/2 LIBRETTO-001 trial.
- The 2-year OS rate observed in this study was consistent with that observed in the Phase 1/2 LIBRETTO-001 trial.
- The most common AEs observed in the real-world were consistent with AEs observed in the LIBRETTO-001 and LIBRETTO-431 trials.
- The relatively lower rates of AEs and SAEs observed in this study may reflect real-world reporting practices.

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BACKGROUND

- Selpercatinib is a highly selective REarranged during Transfection (*RET*)- targeted tyrosine-kinase inhibitor (TKI), recently approved to treat advanced *RET*-fusion-positive NSCLC [1-2].
- Selpercatinib is approved in multiple countries for the treatment of advanced or metastatic *RET*-altered lung or thyroid cancers (TC) [3].
- Marketing authorisation for selpercatinib was granted by the EMA in February 2021 and it became commercially available thereafter in European countries [4].
- Selpercatinib demonstrated therapeutic benefit in pre-treated (LIBRETTO-001 trial) and treatment-naïve (LIBRETTO-001 and LIBRETTO-431 trials) patients with *RET*-fusion-positive NSCLC [5].
- Real-world evidence describing treatment patterns and outcomes for patients treated with selpercatinib in Europe is limited.

METHODS

- SPRINT-RET is a European multi-country, observational, retrospective study of selpercatinib-treated patients with advanced *RET* fusion-positive NSCLC, *RET* fusion-positive thyroid cancer, or *RET* mutation-positive medullary thyroid cancer (MTC) in real-world clinical practice.
- This interim analysis included patients with *RET* fusion-positive NSCLC across Austria, Germany, Netherlands, Spain, and UK.
- Data presented here were collected between April 2023-March 2024 and analysed descriptively.
- Data was collected through a manual chart review of medical records of patients who had received selpercatinib in routine clinical practice during the management of advanced or metastatic disease and who fulfilled the eligibility criteria.
- Disease progression was defined by the treating physician and confirmed either through radiographic or clinical assessment, and documented in the patient's chart.
- Kaplan-Meier method was used to describe time to-event-outcomes, which were measured from initiation of selpercatinib (index date). The outcomes described were as listed and defined below:
  - **Real-world progression-free survival (rwPFS):** Time (in months) from the index date to the date of first documented progression before the end date of the treatment line or ≤30 days after selpercatinib end date or death from any cause
  - **Real-world time to response (rwTTR):** Time (in months) from index date to the date of first documented complete response (CR) or partial response (PR) after the index date, before discontinuation of selpercatinib.
  - **Real-world duration of response (rwDOR):** Time (in months) from date of first documented response (CR or PR) after index date to the first documented progression before selpercatinib end date or ≤30 days after selpercatinib end date or death from any cause.
  - **Overall survival (OS):** Time (in months) between date of selpercatinib treatment initiation (index date) and date of death from any cause.
  - **Real-world overall response rate (rwORR):** Proportion of patients with a best response documented as response (CR or PR).
  - **Real-world disease control rate (rwDCR):** Proportion of patients with a best response documented as CR, PR or SD response.

Inclusion criteria – patients who:

- Received at least one dose of selpercatinib.
- Had a diagnosis of advanced *RET*-fusion positive NSCLC, *RET*-fusion positive TC or *RET*-mutated MTC.
- Were age ≥ 18 years at index date (date of treatment initiation with selpercatinib)
- Provided written informed consent for study data collection or ICF waiver obtained.

Exclusion criteria – patients who:

- Did not have the specified minimum information* available from their hospital medical records.
- Received selpercatinib for the treatment of early-stage disease.
- Received selpercatinib in a clinical trial (LIBRETTO-001, - 431, -531, -432, -121).

*Gender, age, date of diagnosis of advanced disease (locally advanced or metastatic cancer).

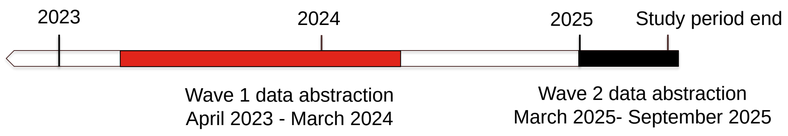


Figure 1: Study outline

Abbreviation: ICF= Informed consent form

KEY RESULT

Table 1: Characteristics of *RET* fusion-positive NSCLC patients and selpercatinib treatment.

	Overall (N=29)*
Patient and tumour characteristics	
Age, median (range)	67.6 (40.9-82.3)
Female (%)	62.1
Smoking status, n (%)	
Current or former smoker	11 (47.8)
Never smoker	12 (52.2)
Missing (n)	6
Disease stage at initial diagnosis, n (%)	
I-IIIa	8 (27.6)
IIIb-c	2 (7.1)
IVa	11 (39.3)
IVb	7 (25.0)
Unknown or missing (n)	1
Histological type, n (%)	
Adenocarcinoma	28 (96.6)
Squamous cell carcinoma	1 (3.4)
Metastasis present at or prior to selpercatinib initiation, n (%)	28 (96.6)
CNS metastasis	6 (20.7)
***RET* fusion partner, n (%)**	
KIF5B	17 (65.4)
CCDC6	5 (19.2)
NCOA4	2 (7.7)
Other	2 (7.7)
Follow-up from selpercatinib initiation (months [median (Q1, Q3])	13.5 (5.7, 24.2)
Characteristics of selpercatinib treatment	
LoT in which selpercatinib initiated, n (%)	
1st line	10 (34.5)
2nd line	13 (44.8)
≥3rd line	6 (20.7)
Initial dosing and administration of selpercatinib, n(%)	
160 mg twice daily	23 (79.3)
Concomitant radiotherapy with selpercatinib, n (%)	5 (17.2)
Dose adjustment or treatment delay required during treatment, n (%)	15 (53.6)
Still receiving selpercatinib at end of follow-up, n (%)	20 (69.0)
Duration of treatment, months, (Median [95% CI])**	NR (11.9, NR)
Patients who discontinued selpercatinib, n (%)	9
Disease progression	5 (55.6)
Death	2 (22.2)
Intercurrent illness	1 (11.1)
Other	1 (11.1)

- Most of the patients who received selpercatinib were female (62.1%), never smokers (52.2%), initially diagnosed with stage IV disease (64.3%) of adenocarcinoma histology (96.6%), with a median age of 67.6 years.
- Six patients (20.7%) had CNS metastasis detected at or prior to selpercatinib initiation.
- Most patients had *RET-KIF5B* fusion (65.4%).
- Selpercatinib was most commonly initiated in 2nd line (44.8%) at a dosage of 160 mg twice daily, and some patients (17.2%) received concomitant radiotherapy.
- Most patients (69.0%) were still receiving selpercatinib at the end of follow-up; median duration of treatment was not reached.

*Missing values are excluded from the denominator for % calculation of each valid category in a categorical variable, and from statistics calculation for a numerical variable.
**Kaplan-Meier (KM) with log-log transformation for 95% CI method used.

Abbreviations: CNS = Central nervous system, LoT= Line of therapy, KIF5B = kinesin family member 5B gene, CCDC6 = coiled-coil domain containing 6, NCOA4 = nuclear coactivator 4, NR = Not reached, TRIM24 = Tripartite motif-containing 24, SD = Standard deviation.

KEY RESULT

Table 2: Effectiveness outcomes for patients treated with selpercatinib.

Outcome		Selpercatinib-treated patients (N=29)	Treatment line immediately prior to selpercatinib (N=19)
rwORR	n, (%)	23 (79.3)	5 (29.4)
	(95% CI)*	(60.3, 92.0)	(10.3, 56.0)
rwDCR	n, (%)	26 (89.7)	12 (70.6)
	95% CI)*	(72.6, 97.8)	(44.0, 89.7)
rwPFS	Months, median	25.0	7.1
	(95% CI)**	(10.3, NR).	(2.2, 9.7)
rwTTR	Months, median	2.8	
	(95% CI)**	(2.2, 3.4)	
OS probability at 24 months	Probability (%)	70.0	
	(95% CI)**	(41.3, 86.5)	
Incidence of new CNS metastases during selpercatinib treatment, n (%)***	n (%)***	2 (8.7%)	
		Selpercatinib-treated patients with first response CR/PR (N=22)	
rwDOR	Months, median	22.1	
	(95% CI)**	(6.3, NR)	

*Clopper-Pearson method used.
**Kaplan-Meier (KM) with log-log transformation for 95% CI method used.
***Among 23 of 29 patients who did not have CNS metastases at initiation of selpercatinib.
-Missing values are excluded from the denominator for % calculation of each valid category in a categorical variable, and from statistics calculation for a numerical variable.

Abbreviations: CI = confidence interval, NR = not reached; OS = overall survival, rwDCR = real-world disease control, rwDOR = real-world duration of response, rwORR = real-world overall response rate, rwPFS = real-world progression-free survival, rwTTR = real-world time to response.

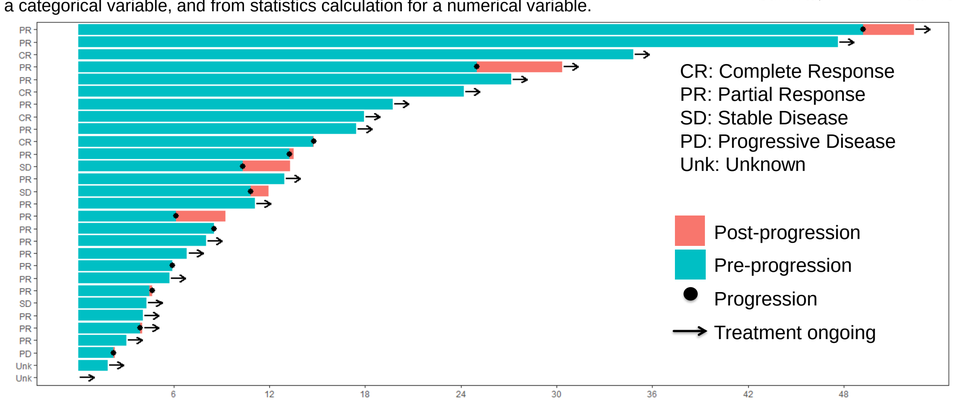


Figure 2: Swimmer plot of duration of selpercatinib treatment and tumour response at patient level.

- The rwORR on selpercatinib treatment was 79.3% (vs. 29.4% on immediate prior line) and the rwDCR was 89.7% (vs. 70.6% on immediate prior line).
- The median rwPFS on selpercatinib was 25.0 (10.3, NR) months, compared to 7.1 (2.2, 9.7) months on the immediate prior line.
- At 24 months, the OS rate was 70%.
- Two (8.7%) of 23 CNS-metastasis-free (at selpercatinib initiation) patients developed brain metastases during selpercatinib treatment.
- Some patients continued to receive selpercatinib after disease progression, with 2 patients still receiving selpercatinib at end of follow-up >3 months after disease progression.

Authors Declarations
Maximilian Hochmair Hochmair reports personal fees for lectures, consultancy, and participation in advisory boards from Amgen, AstraZeneca, Bristol Myers Squibb, Merck, Lilly Oncology,Roche, MSD, Pfizer, and Takeda Oncology; S. Popat has received Consulting fees from: Anheart Therapeutics, Amgen, AstraZeneca, Bayer, Arcus Biosciences, BMS, Boehringer Ingelheim, Ellipses, EQRx, Daiichi Sankyo, Gilead, GSK, Guardant Health, IO Biotech, Janssen, Lilly, Merck Serono, Mirati, MSD, Novocure, Novartis, Pharmamar, Roche, Takeda, Pfizer, Pierre Fabre, Turning Point Therapeutics, and Regeneron; and Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from: AstraZeneca, Bayer, Guardant Health, Janssen, Merck Serono, Roche, and Takeda; Sayed Hashemi reports Research grants and/or advisory roles in AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Janssen, GSK, MSD, Novartis, Roche and Takeda; Tarun Puri, Manoj Khanal and Grace Segall are employees and minor shareholders of Eli Lilly and Company.

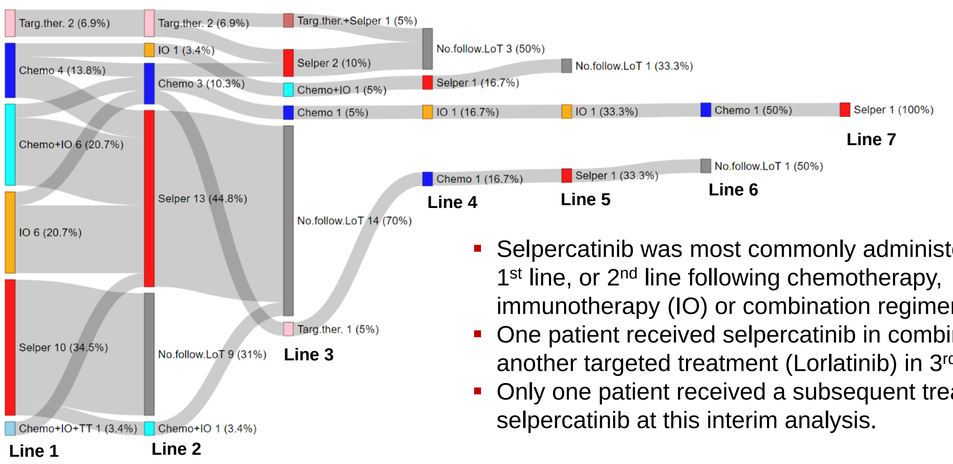
Table 3: Adverse events presented by patients during treatment with selpercatinib

At patient level:	Selpercatinib-treated patients N=29	At AE level	AEs during treatment with selpercatinib N=136
Patients with any AE, n (%)	24 (82.8)	Relatedness to selpercatinib treatment*	
		Related, n (%)	49 (36.0)
Patients with any SAE, n (%)	9 (31.0)	Unrelated, n (%)	26 (19.1)
Patients with any AE grade ≥3, n (%)	12 (41.4)	Unknown, n (%)	61 (44.9)
Most common AEs at patient level, n (%):		Grade	
Fatigue	6 (20.7)	Grade ≥3, n (%)	27 (20.6)
Constipation	5 (17.2)	Unknown grade, n (%)	5 (3.7)
Diarrhoea	5 (17.2)		
Mucosal inflammation	5 (17.2)		

Subjects may be counted in more than one category.

*As determined by the treating physician and documented in the medical record.

- The most commonly reported AE at patient level was fatigue, n= 6 (20.7%).



- Selpercatinib was most commonly administered in either 1st line, or 2nd line following chemotherapy, immunotherapy (IO) or combination regimen.
- One patient received selpercatinib in combination with another targeted treatment (Lorlatinib) in 3rd line.
- Only one patient received a subsequent treatment after selpercatinib at this interim analysis.

Figure 3: Sankey plot of treatment sequence showing all lines of therapy since first LoT in *RET* fusion-positive NSCLC patients.

Abbreviations: Chemo, chemotherapy; IO, immunotherapy; No.follow.LoT, No following line of therapy; Selper, selpercatinib; Targ.Ther, targeted therapy.

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