External control cohorts for the single-arm LIBRETTO-001 trial of selpercatinib in RET+ non-small-cell lung cancer

C. Rolfo1, L. M. Hess2*, M.-H. Jen3, P. Peterson4, X. Li5, H. Liu6, Y. Lai5, T. Sugihara4, U. Kiiskinen5, A. Vickers6 & Y. Summers7

1Center for Thoracic Oncology at Tisch Cancer Center, Mount Sinai Health System & Icahn School of Medicine at Mount Sinai, New York; 2Eli Lilly and Company, Indianapolis, USA; 3Eli Lilly and Company, Basingstoke, UK; 4Syneos Health, Austin, USA; 5Eli Lilly and Company, Helsinki, Finland; 6RTI Inc., Manchester, UK; 7The Christie NHS Foundation Trust, Manchester, UK

Available online 2 August 2022

Background: Data for selpercatinib [a selective REarranged during Transfection (RET) inhibitor] from a single-arm trial (LIBRETTO-001, NCT03157128) in RET-fusion-positive advanced/metastatic non-small-cell lung cancer (NSCLC) were used in combination with external data sources to estimate comparative efficacy [objective response rate (ORR), progression-free survival, and overall survival (OS)] in first- and second-line treatment settings.

Methods: Patient-level data were obtained from a de-identified real-world database. Patients diagnosed with advanced/metastatic NSCLC with no prior exposure to a RET inhibitor and one or more prior line of therapy were eligible. Additionally, individual patient-level data (IPD) were obtained from the pemetrexed + platinum arm of KEYNOTE-189 (NCT03950674, first line) and the docetaxel arm of REVEL (NCT01168973, post-progression). Patients were matched using entropy balancing, doubly robust method, and propensity score approaches. For patients with unknown/negative RET status, adjustment was made using a model fitted to IPD from a real-world database.

Results: In first-line unadjusted analyses of the real-world control, ORR was 87.2% for LIBRETTO-001 versus 66.7% for those with RET-positive NSCLC (P = 0.06). After adjustment for unknown RET status and other patient characteristics, selpercatinib remained significantly superior versus the real-world control for all outcomes (all P < 0.001 except unadjusted RET-fusion-positive cohort). Similarly, outcomes were significantly improved versus clinical trial controls (all P < 0.05).

Conclusions: Findings suggest improvement in outcomes associated with selpercatinib treatment versus the multiple external control cohorts, but should be interpreted with caution. Data were limited by the rarity of RET, lack of mature OS data, and uncertainty from assumptions to create control arms from external data.

Key words: external control, real-world data, synthetic control, clinical trial, RET fusion

INTRODUCTION

Selpercatinib is being studied in an ongoing phase I/II clinical trial in patients with advanced solid tumors (LIBRETTO-001; NCT03157128). RET alterations occur in a number of solid tumors and are the oncogenic drivers for 1%-2% of all non-small-cell lung cancers (NSCLCs). The primary endpoint of the phase II portion of LIBRETTO-001 is to assess the antitumor activity of selpercatinib by determining objective response rate (ORR). Secondary objectives include progression-free survival (PFS) and overall survival (OS). The most recent analyses of LIBRETTO-001 observed an ORR of 85% in the treatment-naïve, 64% in the primary analysis set (PAS) of the first 105 consecutively enrolled patients, and 57% in the integrated analysis set (IAS) of all patients with prior platinum-based therapy. Estimated median PFS was 19.3 months in both the PAS and IAS but was not reached among patients who were treatment-naïve at study enrollment.

Due to the single-arm design of LIBRETTO-001, direct comparisons to other therapies cannot be made without applying appropriate statistical methods to account for differences in patient populations and other factors that could impact the observed outcomes. This study was designed to apply multiple approaches to balance the LIBRETTO-001 with patient-level data from a real-world database and individual patient data (IPD) from the control arms from two separate clinical trials for comparisons against standard-of-care treatments for patients with advanced or metastatic NSCLC.
MATERIALS AND METHODS

Patient-level electronic health record data were used as a real-world control cohort to conduct comparative effectiveness analyses of a blended comparator of multiple standard therapies versus the PAS and treatment-naive cohorts of LIBRETTO-001. For the real-world cohort, RET status was known. Patient-level clinical trial data were used to conduct comparative efficacy analyses versus the treatment-naive, PAS, and IAS cohorts of LIBRETTO-001. RET status was unknown for the clinical trial cohorts.

Real-world external control

The nationwide (US-based) Flatiron Health—Foundation Medicine Clinico-Genomics Database (CGDB) was used to select real-world control cases for this study. Briefly, the CGDB is a linked retrospective database of patients with longitudinal electronic health record (EHR)-derived data from Flatiron Health, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and linked to genomic data derived from Foundation Medicine, Inc. (FMI) comprehensive genomic profiling tests by de-identified, deterministic matching. Data in the CGDB are de-identified and subject to obligations to prevent re-identification and protect patient confidentiality. Institutional review board approval of the real-world cohort was obtained by Flatiron Health before study conduct, and included a waiver of informed consent.

Eligible patients were diagnosed with advanced or metastatic NSCLC and had at least two observations in the CGDB on or after 1 January 2011, had a RET fusion, no evidence of other genomic alterations (EGFR, ALK, ROS1, BRAF, or KRAS), evidence of initiating systemic anticancer therapy on or after May 2017 (consistent with the enrollment time period for LIBRETTO-001), and had no evidence of receiving any selective RET inhibitor at any time. For the PAS cohort match, at least two lines of therapy must have been recorded. Patients meeting eligibility criteria within the CGDB were assigned to the external control group in the primary analysis, Analytic Strategy 1. Follow-up data were available through the end of March 2021.

Analytic Strategy 2 addressed the limitation of the known rarity of RET fusions and the lack of evidence to date suggesting there is a unique prognostic effect thereof by removing the eligibility requirement for a RET fusion from Analytic Strategy 1. Analytic Strategy 3 used the larger CGDB cohort, but applied an adjustment factor for RET.

RET adjustment factor. The potential impact of RET fusions was explored by fitting multivariable acceleration failure time models to CGDB data with multiple imputation of missing data to obtain an estimate of the time acceleration factor for RET-fusion-positive status, after taking into account age, sex, race, stage, smoking status, ECOG performance status, histology, and the drug class used in first-line treatment. For the first-line setting, time since initial diagnosis was included as a factor, whereas in the post-progression setting the time from first- to second-line therapy was included. Point estimates of the time acceleration factors were used to adjust the survival times for PFS (first-line and post-progression settings) and OS (post-progression) for patients without RET fusions. It was not possible to estimate ORR for Analytic Strategy 3 using the methods described earlier, as tumor response is not a continuous variable.

Statistical analysis. Comparative analyses adjusted for any resulting imbalances in patient characteristics between LIBRETTO-001 and real-world control cohorts by applying entropy balancing.10 Separate analyses were conducted for patients who received selpercatinib in the first-line setting versus later-lines of therapy. The covariates included in this procedure were: sex (male versus female), age at start of first-line therapy, ECOG performance status (0 versus >0), smoking status (never versus ever), tumor histology (non-squamous versus squamous versus missing), disease stage at initial diagnosis (IV versus I-III), time from advanced/metastatic diagnosis to start of the comparator treatment, and patient body weight. Imputation of missing values within the CGDB was applied as follows: for missing categorical values of sex, ECOG performance status, histology, smoking status, and stage at diagnosis, imputed randomly based on the cohort overall proportions of each variable, respectively. For missing continuous variables of age, time from diagnosis, or body weight, the mean value for the cohort was used for imputation. Weights obtained from entropy balancing were normalized to sum to the original number of patients in the cohort for whom the weights were applied.

The primary outcome analysis was ORR (complete response + partial response) as recorded in the data source. Unweighted and entropy-balanced time-to-event analyses of PFS and OS were conducted by Kaplan-Meier estimation for within-cohort parameters (medians, quartiles, 1-year rates, 2-year rates). Cox proportional hazards models were utilized for estimation of between-cohort hazard ratios (HRs). Death dates in the CGDB are a composite measure of vital statistics data, and include only month and year to protect patient privacy.11 In the case of Analytic Strategy 3, variables were re-censored at the end of the database, so that the follow-up times did not exceed the endpoint of the original dataset after applying the acceleration factor. OS could not be evaluated in the first-line setting due to lack of mature data from LIBRETTO-001.

Sensitivity analyses were conducted limiting the external control cohort to patients who received platinum-based therapy in the first line for those who were treatment-naive before the index treatment and to those who had received prior platinum-based chemotherapy for the post-progression analyses. All analyses utilizing the real-world cohorts were conducted using SAS Enterprise Guide.

Clinical trial controls

Two separate control cohorts were constructed using IPD from the control arms of KEYNOTE-189 and REVEL trials. The
most current IPD available to the investigators were the de-identified pemetrexed + platinum-based chemotherapy arm of the KEYNOTE-189 trial (clinicaltrials.gov identifier: NCT02578680) and the docetaxel arm (restricted to patients with non-squamous disease) of the REVEL trial (clinicaltrials.gov identifier: NCT01168973). All patient data used in this study were collected after patients provided informed consent and additional de-identification measures applied.

Patients enrolled to KEYNOTE-189 had metastatic NSCLC and were treatment-naïve at the time of enrollment. Patients enrolled to the REVEL trial had received prior platinum-based therapy and had progressive disease. Neither cohort had data or tissue available to determine RET status. The time periods for clinical trial enrollment were 2016 to 2017 (KEYNOTE-189) and 2010 to 2013 (REVEL). Due to the non-contemporaneous enrollment time periods and absence of genomic alteration data, an adjustment was made to account for RET status for the primary analysis, similar to real-world Analytic Strategy 3 as described earlier.

Patient data from the clinical trial control cohorts were matched to LIBRETTO-001 based on covariates present in both datasets (age, ECOG performance status, smoking status, sex, race and stage at initial diagnosis, and for the REVEL control arm, time since diagnosis to start of the index therapy) using targeted maximum likelihood estimation (TMLE), a doubly robust method which makes use of IPD from each dataset to fit regression-based models simultaneously to both groups. TMLE leverages ensemble machine-learning techniques to estimate parameters in a flexible manner, and cross-validation was used to select the best-performing estimator from a library of candidate estimators. The analysis was implemented in the survtmle package in R. IPD were reconstructed by digitizing the adjusted Kaplan–Meier graphs for TMLE for the pemetrexed + platinum arm of the KEYNOTE-189 trial versus patients who were treatment-naïve in LIBRETTO-001 and for the docetaxel arm from the REVEL trial versus the pre-treated IAS and PAS cohorts from LIBRETTO-001. Cox regression models plus a nonparametric log-rank test were applied to the reconstructed data to compare time-to-event treatment outcomes. This methodological approach could not be applied to the estimation of ORR as this is a categorical variable. OS comparisons were not conducted in the first-line setting due to highly immature data from LIBRETTO-001.

Sensitivity analyses of the comparisons between LIBRETTO-001 and clinical trial control cohorts were conducted by alternatively matching using propensity score methods, matching using a genetic algorithm, propensity score weighting (PSW) based on logistic regression, and boosted PSW based on logistic regression with interaction. All time-to-event analyses were conducted in R using Cox regression models and nonparametric log-rank test on the trial-matched datasets. Statistical significance was based on two-sided statistical testing ($\alpha \leq 0.05$).

RESULTS

Real-world external control
For the first-line setting, 29 patients met eligibility criteria for Analytic Strategy 1 ($n = 22$, 75.9% of whom received a checkpoint inhibitor as part of the regimen), 2791 for Analytic Strategies 2 and 3 ($n = 1703$, 61.0% received a checkpoint inhibitor as part of the regimen), and 985 (all of whom received a checkpoint inhibitor with the platinum-based first-line therapy, 100%) were included in the sensitivity analysis (platinum-based chemotherapy comparator).

For the post-progression setting, a total of 17 patients met eligibility criteria for Analytic Strategy 1, 1503 for Analytic Strategies 2 and 3 (real-world blended comparators), and 720 for the sensitivity analyses (prior platinum-based chemotherapy comparator). The characteristics of these cohorts, before and after entropy balancing, are summarized in Table 1.

RET adjustment factor. Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100551, presents the parameters applied to the RET adjustment of the real-world control cohort in Analytic Strategy 3 and for the KEYNOTE-189 and REVEL clinical trial control cohorts. Patients without RET fusions receiving selpercatinib in the first-line setting had their PFS increased by a factor of 1.53. In the post-progression setting, OS was increased by a factor of 1.65 and PFS by 1.2 with selpercatinib. The RET adjustment factors were applied to each patient without a RET fusion to account for any potential prognostic improvement in outcomes that could be due to positive RET fusion status. Patients whose events were forecasted to future events (beyond the database lock/end date) were censored at the end of the follow-up period, with re-censoring as described earlier.

Tumor response. Tumor response is summarized in Table 2 for the first-line and the post-progression settings versus the real-world control. Entropy balancing could not be applied to Analytic Strategy 1 due to small sample size. All entropy-balanced comparisons showed a significant improvement in ORR for patients treated with selpercatinib in LIBRETTO-001 versus the real-world control (all comparisons were statistically significant at $P < 0.001$).

Progression-free survival. PFS outcomes are presented in Table 3 for the real-world control analyses. In the first-line setting, PFS was significantly improved for patients treated with selpercatinib on the LIBRETTO-001 trial versus the real-world control unweighted comparisons using Analytic Strategy 1 [HR = 0.31, 95% confidence interval (CI) 0.16-0.64, $P = 0.0007$]. Median PFS was not reached in the selpercatinib group (95% CI 11.5-not reached) versus 6.7 months (95% CI 3.7-12.1 months) for the real-world control. Entropy balancing was not possible for Analytic Strategy 1 due to small sample size. There were statistically significant differences in the entropy-balanced approaches for Analytic Strategy 2, Analytic Strategy 3, and all sensitivity analyses.
### Table 1. Baseline characteristics of patients treated with selpercatinib (LIBRETTO-001 trial) and the real-world control, before and after entropy balancing

| Characteristic                              | Selpercatinib cohort (LIBRETTO-001) | Post-progression setting, before entropy balancing | Post-progression setting, after entropy balancinga |
|---------------------------------------------|-------------------------------------|---------------------------------------------------|--------------------------------------------------|
|                                             | Real-world control Analytic Strategy 1 (RET fusion positive) | Real-world control Analytic Strategies 2 and 3 | Real-world control sensitivity analysis |
|                                             | Selpercatinib cohort (LIBRETTO-001) | Selpercatinib cohort (LIBRETTO-001) | Selpercatinib cohort (LIBRETTO-001) |
| N                                           | 48                                  | 29                                                 | 2791                                             | 2791                             |
| NOS, n (%)                                   | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Sex, n (%)                                   | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Female                                       | 29 (60.4)                           | 13 (44.8)                                          | 1132 (40.6)                                      | 369 (37.5)                        |
| Male                                         | 19 (39.6)                           | 16 (55.2)                                          | 1659 (59.4)                                      | 516 (62.5)                        |
| Age, mean (SD)                               | 62.2 (14.1)                         | 65.6 (12.0)                                        | 68.8 (9.5)                                       | 68.8 (9.3)                        |
| Body weight, mean kg (SD)                   | 71.7 (18.1)                         | 75.8 (16.3)                                        | 75.8 (19.3)                                      | 75.8 (18.6)                       |
| ECOG performance status, n (%)              | 0                                   | 0                                                  | 0                                                 | 0                                 |
| History of smoking, n (%)                   | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Stage at initial diagnosis, n (%)            | 0                                   | 0                                                  | 0                                                 | 0                                 |
| I-III                                        | 4 (8.3)                             | 8 (27.6)                                           | 1126 (40.3)                                      | 213 (21.6)                        |
| IV                                           | 43 (89.6)                           | 21 (72.4)                                          | 1600 (57.3)                                      | 754 (76.5)                        |
| Missing                                      | 1 (2.1)                             | 0                                                  | 65 (2.3)                                         | 18 (1.8)                          |
| Tumor histology, n (%)                       | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Non-squamous                                 | 43 (89.6)                           | 29 (100.0)                                         | 1571 (56.3)                                      | 647 (65.7)                        |
| Squamous                                     | 0                                   | 0                                                  | 1075 (38.5)                                      | 285 (28.9)                        |
| NOS                                          | 5 (10.4)                            | 0                                                  | 145 (5.2)                                        | 53 (5.4)                          |
| Presence of brain metastases, n (%)          | 3 (6.3)                             | 5 (17.2)                                           | 415 (14.9)                                       | 178 (18.1)                        |
| Time from advanced/metastatic diagnosis to index therapy, mean (SD) days | 62.2 (46.5) | 115.7 (277.3) | 105.2 (277.7) | 71.0 (235.7) |

---

### Table 1. Baseline characteristics of patients treated with selpercatinib (LIBRETTO-001 trial) and the real-world control, before and after entropy balancing (continued)

| Characteristic                              | Selpercatinib cohort (LIBRETTO-001, PAS) | Post-progression setting, before entropy balancing | Post-progression setting, after entropy balancinga |
|---------------------------------------------|----------------------------------------|---------------------------------------------------|--------------------------------------------------|
|                                             | Real-world control Analytic Strategy 1a | Real-world control Analytic Strategies 2 and 3 | Real-world control sensitivity analysis |
|                                             | Selpercatinib cohort (LIBRETTO-001, PAS) | Selpercatinib cohort (LIBRETTO-001, PAS) | Selpercatinib cohort (LIBRETTO-001, PAS) |
| N                                           | 105                                  | 17                                                 | 1503                                             | 1503                             |
| NOS, n (%)                                   | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Sex, n (%)                                   | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Female                                       | 62 (59.0)                            | 10 (58.8)                                          | 619 (41.2)                                       | 305 (42.4)                        |
| Male                                         | 43 (41.0)                            | 7 (41.2)                                           | 884 (58.8)                                       | 415 (57.6)                        |
| Age, mean (SD)                               | 58.6 (11.9)                          | 65.6 (11.8)                                        | 68.9 (9.5)                                       | 68.5 (9.3)                        |
| Body weight, mean kg (SD)                   | 67.8 (17.4)                          | 70.2 (12.8)                                        | 75.0 (18.7)                                      | 75.1 (19.6)                       |
| ECOG performance status, n (%)              | 0                                   | 0                                                  | 0                                                 | 0                                 |
| History of smoking, n (%)                   | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Stage at initial diagnosis, n (%)            | 0                                   | 0                                                  | 0                                                 | 0                                 |
| I-III                                        | 4 (3.8)                             | 4 (23.5)                                           | 659 (43.8)                                       | 291 (40.4)                        |
| IV                                           | 101 (96.2)                           | 13 (76.5)                                          | 807 (53.7)                                       | 410 (56.9)                        |
| Missing                                      | 0                                   | 0                                                  | 37 (2.5)                                         | 19 (2.6)                          |
| Tumor histology, n (%)                       | 0                                   | 0                                                  | 0                                                 | 0                                 |
| Non-squamous                                 | 92 (87.6)                           | 17 (100.0)                                         | 829 (55.2)                                       | 382 (53.1)                        |
| Squamous                                     | 1 (1.0)                             | 0                                                  | 605 (40.3)                                       | 307 (42.6)                        |
| NOS                                          | 12 (11.4)                           | 0                                                  | 69 (4.6)                                         | 31 (4.3)                          |
| Presence of brain metastases, n (%)          | 11 (10.5)                            | 3 (17.6)                                           | 262 (17.4)                                       | 129 (17.9)                        |
| Time from metastatic diagnosis to index therapy, mean (SD) days | 856.5 (692.5) | 690.9 (665.3) | 470.5 (575.6) | 443.6 (557.6) |

---

Analytic Strategy 1: patients with RET fusion-positive disease; Analytic Strategy 2: all patients, regardless of RET fusion status; Analytic Strategy 3: all patients, regardless of RET fusion status and applying the RET adjustment factor; sensitivity analysis: all patients who had received prior platinum-based therapy.

ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise stated; PAS, Primary analysis set; RET, REarranged during Transfection; SD, standard deviation.

aDue to the small sample size, entropy balancing could not be applied to Analytic Strategy 1.
(Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100551). In the entropy-balanced analysis for Analytic Strategy 2, the median PFS for selpercatinib was not reached (95% CI 11.5-not reached) and for the real-world control, median PFS was 5.6 months (95% CI not evaluable), with a HR of 0.21 (95% CI 0.19-0.24, P < 0.0001). These results were similar in the first line for the RET-adjusted entropy-balanced Analytic Strategy 3, where the median PFS was not reached for selpercatinib (95% CI 11.5-not reached) versus a median PFS of 8.3 months (95% CI not evaluable) for the real-world control (HR = 0.31, 95% CI 0.27-0.35, P < 0.0001). Sensitivity analyses limiting to platinum-based therapy in the real-world control (HR = 0.24, 95% CI 0.24-0.34, P = 0.0002; RET-adjusted HR = 0.34; 95% CI 0.28-0.41, P = 0.0001) also showed significant differences. The Kaplan—Meier curves for all PFS analyses in the first-line setting are presented in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100551.

In the post-progression setting (Table 3), PFS was significantly improved for patients treated with selpercatinib on the LIBRETTO-001 trial versus the real-world control in unweighted comparisons for Analytic Strategy 1 (HR = 0.29, 95% CI 0.16-0.53, P < 0.0001). Estimated median PFS was 19.3 months (95% CI 13.9 months-not reached) for those treated with selpercatinib versus 4.0 months (95% CI 2.0-12.2 months) for the real-world control. Similar to the first-line setting, there was insufficient sample size to perform entropy balancing. There remained statistically significant differences amongst unweighted and entropy-balanced Analytic Strategies 2 and 3 in sensitivity analyses (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100551). In the entropy-balanced analysis for Analytic Strategy 2, the median PFS for selpercatinib was 19.3 months (95% CI 13.9 months-not reached) and for the real-world control was 4.3 months (95% CI not evaluable), with a HR of 0.27 (95% CI 0.24-0.31, P < 0.0001). These results were similar when applying the RET adjustment factor to the real-world cohort in Analytic Strategy 3, which shows a median PFS of 19.3 months (95% CI 13.9 months-not reached) for patients treated with selpercatinib versus a median PFS of 5.2 months (95% CI not evaluable) for the real-world control (HR = 0.31, 95% CI 0.28-0.36, P < 0.0001). Sensitivity analyses limiting Analytic Strategy 2 to prior platinum-based therapy results were similar (HR = 0.28, 95% CI 0.24-0.34, P = 0.0002), as was applying the RET adjustment factor to the sensitivity analysis (HR = 0.33, 95% CI 0.27-0.39, P = 0.0005). The Kaplan—Meier curves for all PFS outcomes in the post-progression setting are presented in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100551.

Overall survival. The median duration of follow-up for patients enrolled in LIBRETTO-001 at the time of this analysis was 15.7 months (PAS) and 12.0 months (IAS) amongst patients who received prior platinum-based therapy and 9.8 months for those who were treated with selpercatinib in the first-line setting. OS in the post-progression setting is presented in Table 3. Median OS was not reached in either the

### Table 2. Tumor response of selpercatinib (LIBRETTO-001) versus real-world control

| Outcome | First-line setting, before entropy balancing | First-line setting, after entropy balancing |
|---------|---------------------------------------------|--------------------------------------------|
| ORR, Analytic Strategy 1 | Selpercatinib Cohort (LIBRETTO-001) (n = 48) 41 (87.2) P = 0.06 | Real-world control (N = 29) 12 (66.7) |
| ORR, Analytic Strategy 2 | Selpercatinib Cohort (LIBRETTO-001) (N = 48) 11.5 (not reached) P < 0.0001 | Real-world control (N = 2791) 891 (59.2) |
| ORR, sensitivity analysis | Selpercatinib cohort (LIBRETTO-001) (N = 48) 41 (87.2) P = 0.002 | Real-world control (N = 985) 479 (65.6) |

| Outcome | Post-progression, before entropy balancing | Post-progression, after entropy balancing |
|---------|---------------------------------------------|--------------------------------------------|
| ORR, Analytic Strategy 1 | Selpercatinib cohort (LIBRETTO-001) (N = 105) 67 (67.7) P = 0.004 | Real-world control (N = 17) 3 (25.0) |
| ORR, Analytic Strategy 2 | Selpercatinib cohort (LIBRETTO-001) (N = 105) 67 (67.7) P < 0.0001 | Real-world control (N = 1503) 263 (35.6) |
| ORR, sensitivity analysis | Selpercatinib cohort (LIBRETTO-001) (N = 105) 67 (67.68) P < 0.0001 | Real-world control (N = 720) 129 (33.86) |

Analytic Strategy 1: patients with RET fusion-positive disease; Analytic Strategy 2: all patients, regardless of RET fusion status; Analytic Strategy 3: all patients, regardless of RET fusion status and applying the RET adjustment factor; sensitivity analysis: all patients who had received prior platinum-based therapy.

NA, not available; ORR, objective response rate; RET, REarranged during Transfection.
LIBRETTO-001 or real-world control cohorts in Analytic Strategy 1, and adjusted analyses could not be conducted due to the lack of events (censoring rates were 73.3% in LIBRETTO-001 and 76.5% in the real-world cohort). Median OS in Analytic Strategy 2 (entropy-balanced) for the post-progression setting was not reached among patients treated with selpercatinib (95% CI 25.7-not reached), and was 10.6 months in the real-world cohort (95% CI not evaluable), with a HR of 0.25 (95% CI 0.21-0.29, P < 0.0001). These results were similar for Analytic Strategy 3; the median OS was not reached among patients treated with selpercatinib versus a median OS of 16.8 months (95% CI not evaluable) for the real-world control in the entropy-balanced analysis (HR = 0.38, 95% CI 0.32-0.45, P = 0.001). Sensitivity analyses found consistent results in the post-progression setting compared with patients in the real-world cohort who were treated with platinum-based therapy, with a HR of 0.21 (95% CI 0.17-0.26, P < 0.0001) and for the RET-adjusted sensitivity analysis, with a HR = 0.31 (95% CI 0.25-0.39, P = 0.001). The Kaplan–Meier curves for all OS analyses in the post-progression setting are presented in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100551.

| Table 3. Progression-free survival (PFS) and overall survival (OS) of selpercatinib (LIBRETTO-001) versus real-world control |
|---------------------------------|-----------------|-----------------|-----------------|
| **PFS, first-line setting**     | Median months (95% CI) | HR (95% CI) | P value |
| Analytic Strategy 1             |                  |                |                |
| Selpercatinib                  | NA (11.5-NA)    | 0.31 (0.16-0.64) | 0.0007 |
| Real-world control              | 6.7 (NA)        |                |                |
| Analytic Strategy 2             |                  |                |                |
| Selpercatinib                  | NA (11.5-NA)    | 0.21 (0.19-0.24) | <0.0001 |
| Real-world control              | 5.6 (NA)        |                |                |
| Analytic Strategy 3             |                  |                |                |
| Selpercatinib                  | NA (11.5-NA)    | 0.31 (0.27-0.35) | <0.0001 |
| Real-world control              | 8.3 (NA)        |                |                |
| Sensitivity analysis of Analytic Strategy 2 | 19.3 (13.9-NA) | 0.28 (0.24-0.34) | 0.0002 |
| Selpercatinib                  | 3.6 (NA)        |                |                |
| Platinum-based therapy          | 19.3 (13.9-NA)  | 0.34 (0.28-0.41) | 0.0001 |
| Platinum-based therapy          | 9.3 (NA)        |                |                |
| **PFS, post-progression**       | Median months (95% CI) | HR (95% CI) | P value |
| Analytic Strategy 1             |                  |                |                |
| Selpercatinib                  | 19.3 (13.9-NA)  | 0.29 (0.16-0.53) | <0.0001 |
| Real-world control              | 4.0 (2.0-12.2)  |                |                |
| Analytic Strategy 2             |                  |                |                |
| Selpercatinib                  | 19.3 (13.9-NA)  | 0.27 (0.24-0.32) | <0.0001 |
| Real-world control              | 4.3 (NA)        |                |                |
| Analytic Strategy 3             |                  |                |                |
| Selpercatinib                  | 19.3 (13.9-NA)  | 0.31 (0.28-0.36) | <0.0001 |
| Real-world control              | 5.2 (NA)        |                |                |
| Sensitivity analysis of Analytic Strategy 2 | 19.3 (13.9-NA) | 0.28 (0.24-0.34) | 0.0002 |
| Selpercatinib                  | 3.6 (NA)        |                |                |
| Prior platinum-based therapy    | 19.3 (13.9-NA)  | 0.33 (0.27-0.39) | 0.0005 |
| Prior platinum-based therapy    | 4.3 (NA)        |                |                |
| **OS, post-progression**        | Median months (95% CI) | HR (95% CI) | P value |
| Analytic Strategy 1             |                  |                |                |
| Selpercatinib                  | NA (25.7-NA)    | 0.95 (0.33-2.73) | 0.92 |
| Real-world control              | NA (15.2-NA)    |                |                |
| Analytic Strategy 2             |                  |                |                |
| Selpercatinib                  | NA (25.7-NA)    | 0.25 (0.21-0.29) | <0.0001 |
| Real-world control              | 10.6 (NA)       |                |                |
| Analytic Strategy 3             |                  |                |                |
| Selpercatinib                  | NA (25.7-NA)    | 0.38 (0.32-0.45) | 0.001 |
| Real-world control              | 16.8 (NA)       |                |                |
| Sensitivity analysis of Analytic Strategy 2 | NA (25.7-NA)  | 0.21 (0.17-0.26) | <0.0001 |
| Selpercatinib                  | 9.0 (NA)        |                |                |
| Prior platinum-based therapy    | NA (25.7-NA)    | 0.31 (0.25-0.39) | 0.001 |
| Prior platinum-based therapy    | 14.9 (NA)       |                |                |
### Table 4. Baseline characteristics of patients treated with selpercatinib (LIBRETTO-001) and clinical trial controls (KEYNOTE-189, first-line setting; REVEL, post-progression setting), before and after matching

| Characteristic | Before adjustment or matching, first-line setting | After matching using propensity scoring | After matching using a genetic algorithm | After PSW using a generalized boosted model | After PSW using logistic regression |
|---------------|---------------------------------|--------------------------------------|----------------------------------------|-------------------------------------------|----------------------------------|
|                | Selpercatinib cohort (LIBRETTO-001) n = 48<sup>a</sup> | Pemetrexed + platinum cohort (KEYNOTE-189) n = 206 | Pemetrexed + platinum cohort (KEYNOTE-189) n = 44 | Pemetrexed + platinum cohort (KEYNOTE-189) n = 36 | Pemetrexed + platinum cohort (KEYNOTE-189) n = 40 |
| Age (mean, years) | 60.9 | 63.5 | 63.0 | 63.6 | 60.9 | 62.7 |
| Female, % | 59.1 | 47.1 | 45 | 54.4 | 54.5 | 56.9 |
| Race: White, % | 72.8 | 94.2 | 75 | 72.7 | 75.6 | 77.7 |
| Race: Asian, % | 18.2 | 3.9 | 18 | 27.3 | 20.4 | 20.1 |
| Race: Other, % | 9.1 | 0.2 | 7 | 0 | 4 | 2.2 |
| Never smoker, % | 68.2 | 12.1 | 57 | 65.9 | 67.7 | 67.2 |
| Stage IV, % | 93.2 | 99.5 | 98 | 95.5 | 99.2 | 97.8 |
| ECOG PS ≥ 1, % | 54.5 | 60.7 | 59 | 63.3 | 56.6 | 60.8 |

| Characteristic | Before adjustment or matching, post-progression setting | After matching using propensity scoring | After matching using a genetic algorithm | After PSW using a generalized boosted model | After PSW using logistic regression |
|---------------|---------------------------------|--------------------------------------|----------------------------------------|-------------------------------------------|----------------------------------|
|                | Selpercatinib cohort (LIBRETTO-001) n = 218<sup>b</sup>Docetaxel cohort (REVEL) n = 447 | Docetaxel cohort (REVEL) n = 207 | Docetaxel cohort (REVEL) n = 207 | Docetaxel cohort (REVEL) n = 120 | Docetaxel cohort (REVEL) n = 82 |
| Age (mean, years) | 58.75 | 59.83 | 59.03 | 59.93 | 59.61 | 59.0 |
| Female, % | 59.2 | 38.4 | 43 | 65.21 | 55.9 | 48.0 |
| Race: White, % | 53.4 | 79.1 | 58 | 49.28 | 53.3 | 52.6 |
| Race: Asian, % | 38.8 | 14.2 | 29 | 41.54 | 36.1 | 31.7 |
| Race: Other, % | 7.8 | 6.7 | 13 | 9.18 | 10.6 | 9.8 |
| Never smoker, % | 71.8 | 25.9 | 53 | 60.39 | 60.6 | 54.8 |
| Stage IV, % | 96.1 | 86 | 94 | 92.75 | 93.0 | 92.5 |
| ECOG PS ≤ 1, % | 72.8 | 68.3 | 63 | 61.84 | 66.0 | 64.1 |
| Time since diagnosis to start of trial (median months) | 36.63 | 12.04 | 15.61 | 31.08 | 22.61 | 17.6 |

ECOG PS, Eastern Cooperative Oncology Group performance status; PSW, propensity score weighting.

<sup>a</sup>Four patients without non-squamous histology were excluded from further matching process.

<sup>b</sup>Five patients with ECOG PS ≥2 and 6 patients without non-squamous histology were excluded from further matching process.

### Clinical trial controls

The patient characteristics from the LIBRETTO-001 trial and from the KEYNOTE-189 (first-line setting) and REVEL trial (post-progression setting) both before and after each propensity score matching (PSM)/PSW approaches after adjusting for RET status are summarized in Table 4. PFS outcomes using the RET-adjusted data that were simultaneously modeled with matched covariates of selpercatinib (LIBRETTO-001) versus pemetrexed + platinum (KEYNOTE-189) in the first-line setting from TMLE are presented in Supplementary Figures S4 and S5, available at https://doi.org/10.1016/j.esmoop.2022.100551. Based on nonparametric log-rank test of Cox regression models adjusted for covariates, PFS was significantly longer for selpercatinib versus docetaxel (REVEL) in the post-progression setting (HR = 0.39, 95% CI 0.29-0.52, P < 0.00001 for IAS and HR = 0.51, 95% CI 0.36-0.72, P < 0.00001 for PAS). OS was also significantly longer for selpercatinib versus docetaxel in the post-progression setting (HR = 0.51, 95% CI 0.35-0.74, P < 0.00001 for IAS and HR = 0.71, 95% CI 0.48-1.03, P = 0.065 for PAS). Sensitivity analyses in the post-progression setting were also consistent with the primary analysis except for the PSW via logistic regression for OS, where re-weighting failed to appropriately match a number of covariates.

### DISCUSSION

This study applied a variety of statistical and methodological approaches to generate external control data using both real-world and clinical trial control data to compare clinical outcomes to patients in LIBRETTO-001 who were pretreated (PAS and IAS) and treatment-naive. The results of these analyses are highly consistent in demonstrating the statistically significant improvement in clinical outcomes of ORR, PFS and post-progression OS associated with selpercatinib treatment. The findings observed in these external...
control analyses in the first-line setting will undergo confirmation with the forthcoming results of an ongoing phase III randomized trial (LIBRETTO-001, NCT04194944).19

Strengths of the study include an approach to developing control cohorts using both real-world and clinical trial control arm approaches. Multiple methods and approaches were applied to obtain estimates of the comparative outcomes of tumor response, PFS, and post-progression OS based upon receipt of standard treatments for advanced or metastatic NSCLC. This study was designed to incorporate the best methods available at this time that could be applied to these datasets, as well as utilizing a variety of approaches to evaluate consistency of findings across these methods and datasets. A variety of approaches demonstrate the stability of the findings of the benefits of selpercatinib across a wide range of scenarios in both the real-world and clinical trial external control data.

Despite the strengths in the approach taken to build and evaluate these external control cohorts using real-world and clinical trial control data, there are limitations that must be considered in the interpretation of these results, which should be considered exploratory and hypothesis-generating findings. There were substantial differences in the baseline characteristics of the real-world...
and LIBRETTO-001 cohorts. The application of entropy balancing resulted in the application of substantial weighting factors to balance these differences, and alternative choices for normalization of these weights could potentially increase or decrease $P$ values arbitrarily. These aspects of the analysis must be considered in the interpretation of results. The sample size for the RET-fusion-positive real-world control in Analytic Strategy 1 was very small, limiting the ability to conduct entropy-balanced comparative analyses. The small sample size available in the Flatiron Health CGOB was further reduced by the strict application of eligibility criteria to match those of the clinical trial. While this is considered a best practice to reduce bias, allowing more flexibility in these factors (such as expanding the time period to before the recruitment window of LIBRETTO-001) may have improved the sample size. However, relaxing the eligibility criteria to increase sample size may have introduced other biases, and the decision to retain the highest level of rigor in the criteria for the control cohorts was retained as per the study protocol.

The comparability of outcomes from the unweighted analysis with RET-fusion-positive cohort (Analytic Strategy 1) and the entropy-balanced outcomes observed in Analytic Strategy 2 provide some assurance of the lack of meaningful impact of RET fusion status on the observed differences, which remained unchanged in Analytic Strategy 3. The prognostic implications of RET fusions on treatment effectiveness for patients with advanced NSCLC are unknown, and the use of the methods to obtain the acceleration factor is limited, likely subjecting them to some degree of error that further contributes to the uncertainty of the RET adjustment factor estimates.

The real-world control data are also limited by the measurement of tumor response and disease progression. In the LIBRETTO-001 trial, tumor response was evaluated by RECIST criteria. In the real world, tumor response is simply as noted by the oncologist and does not require these criteria to have been met. Therefore, the comparison of ORR and PFS versus the real-world control cohorts may be measuring two very different outcomes. Despite this conceptual difference, work published by Flatiron Health show that the physician-reported response is very comparable to RECIST-based response, demonstrating the potential to leverage real-world cohorts as comparators for single-arm trials.

The comparison of selpercatinib with pemetrexed + platinum, the KEYNOTE-189 control cohort, and docetaxel, the REVEL clinical trial control cohort, was selected due to availability of patient-level data using a single comparator that is relevant for patient care in the first-line and post-progression settings. It is important to point out that in the real-world dataset, all patients receiving platinum-based therapy in the first line received a checkpoint inhibitor as part of the regimen. The findings observed were planned for platinum-based therapy generally, but apply to platinum plus checkpoint inhibitor-based therapy due to the regimens used in everyday practice. Therefore, the study data further suggest the comparative benefits of selpercatinib versus platinum + checkpoint inhibitor therapy for patients with RET fusions in the first-line setting.

The strengths of using clinical trial control data are the comparability of outcomes. For example, PFS was evaluated at 6-week intervals in REVEL and at 8-week intervals in LIBRETTO-001. In the real-world setting, progression is noted at whatever time the patient undergoes a scan or other evaluation for disease progression. The strengths of a clinical trial control cohort comparison also include standardized assessments that adhere to RECIST criteria. In both REVEL and LIBRETTO-001, PFS was defined as the time from randomization until the date of objectively determined progressive disease using RECIST criteria (v1.1) or death due to any cause. LIBRETTO-001 is an ongoing phase II trial, and the comparative analyses using external real-world and REVEL control cohorts were used against data that have yet to fully mature from the ongoing trial. Due to the lack of fully mature data, analyses of OS are limited and should be interpreted with caution. The not-evaluable and wide CIs demonstrate the uncertainty of survival data. While a broad range of comparative analyses suggest significant improvements may be observed versus standard of care for patients with advanced or metastatic NSCLC, definitive conclusions cannot be made from these data alone regarding the comparative efficacy of selpercatinib.

Conclusions

The consistency of results across multiple analyses of the real-world and clinical trial control cohorts suggests that selpercatinib is associated with improved outcomes of tumor response, PFS, and post-progression OS versus standard therapies for NSCLC. Results should be considered exploratory and must be confirmed with the ongoing randomized trial.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Material support in terms of data resources, employee time for analysis and writing, and for software access was provided by Eli Lilly and Company, United States.

DISCLOSURE

LMH, MHJ, UK, YL, XIL, HL, and PP are employees of Eli Lilly and Company. TS and AV are employees of Syneos Health and RTI Inc., respectively. Both Syneos Health and RTI Inc. receive funding from Eli Lilly and Company for statistical and analytic support of outcomes research. YS reports advisory/educational activities for Abbvie, AstraZeneca, Amgen, BMS, EQRX, Eli Lilly and Co., MSD, Roche, Takeda, and Pfizer. CR reports current consulting for EMD Serono, Pfizer, Mirati, Eisai, Daiichi Sankyo, and Sanofi; stock ownership in Novartis; educational activities for AstraZeneca, Roche, and CORE2ED; and research grant funding from Pfizer. CR also serves on a safety advisory board for EMD Serono.
DATA SHARING
Lilly provides access to all individual participant data collected during a clinical trial, after anonymization, with the exception of pharmacokinetic or genetic data. 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, blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org. The real-world data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be made available upon request and are subject to a license agreement with Flatiron Health; interested researchers should contact DataAccess@flatiron.com to determine licensing terms.

REFERENCES
1. Li AY, Mccusker MG, Russo A, et al. RET fusions in solid tumors. Cancer Treat Rev. 2019;81:101911.
2. Drilon A, Oxnard GR, Tan DS, et al. Efficacy of selpercatinib in RET fusion–positive non–small-cell lung cancer. N Engl J Med. 2020;383(9):813-824.
3. Besse B, Drilon AE, Solomon BJ, et al. Updated overall efficacy and safety of selpercatinib in patients (pts) with RET fusion+ non-small cell lung cancer (NSCLC). J Clin Oncol. 2021;39:9065.
4. Fenske DC, Price GL, Hess LM, John WJ, Kim ES. Systematic review of brain metastases in patients with non–small-cell lung cancer in the United States, European Union, and Japan. Clin Lung Cancer. 2017;18(6):607-614.
5. Jiang M, Fares AF, Shesphelovich D, et al. The relationship between body-mass index and overall survival in non-small cell lung cancer by sex, smoking status, and race: a pooled analysis of 20,937 International Lung Cancer Consortium (ILCCO) patients. Lung Cancer. 2020;152:58-65.
6. Mytelka DS, Li L, Benoit K. Post-diagnosis weight loss as a prognostic factor in non-small cell lung cancer. J Cachexia Sarcopenia Muscle. 2018;9(1):86-92.
7. Sterne JA, Hernán MA, Mcaleenan A, Reeves BC, Higgins JP. Assessing risk of bias in a non-randomized study. Cochrane Handbook Syst Rev Interv. 2019:621-641.
8. Suresh K. An overview of randomization techniques: an unbiased assessment of outcome in clinical research. J Hum Reprod Sci. 2011;4(1):8-11.
9. Hess LM, Han Y, Zhu YE, Bhandari NR, Sireci A. Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States. BMC Cancer. 2021;21(1):1-12.
10. Hainmueller J. Entropy balancing for causal effects: a multivariate reweighting method to produce balanced samples in observational studies. Polit Anal. 2012;20:25-46.
11. Zhang Q, Gossai A, Monroe S, Nussbaum NC, Parrinello CM. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. Health Serv Res. 2021;56:1281-1287.
12. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(12):2078-2092.
13. Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384(9944):665-673.
14. Faria R, Hernandez Alava M, Manca A, Waioo A. The use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data. NICE DSU Technical Support Document; 2015:17.
15. Pan W, Bai H. Propensity score interval matching: using bootstrap confidence intervals for accommodating estimation errors of propensity scores. BMC Med Res Methodol. 2015;15(1):1-9.
16. Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. J Stat Softw. 2011;42(7):1-52.
17. Gelman A, Hill J. Data Analysis Using Regression and Multilevel/Hierarchical Models. New York: Cambridge University Press; 2007.
18. Gelman A, Hill J. Data Analysis Using Regression and Multi-level/Hierarchical Models. New York: Cambridge University Press; 2007.
19. Goldhaber SZ, Rosing DR, Pichert JW. Prevalent venous thromboembolism: a public health problem in the United States. Arch Intern Med. 2005;165(18):2059-2067.
20. Cong XF, Yang L, Chen C, Liu Z. KIF5B-RET fusion gene and its correlation with clinicopathological and prognostic features in lung cancer: a meta-analysis. Onco Targets Ther. 2019;12:4533.
21. Ma X, Nussbaum N, Magee K, et al. Comparison of real-world response rate (rwRR) to RECIST-based response rate in patients with advanced non-small cell lung cancer (aNSCLC). Ann Oncol. 2019;30:v651.