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# Matching-adjusted indirect comparison of selpercatinib and pralsetinib in *RET* fusion–positive non–small cell lung cancer

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**ABSTRACT**

**Aims:** Selpercatinib and pralsetinib are approved for RET-rearranged non – small cell lung cancer.
**Materials & methods:** Efficacy and safety were compared using matching-adjusted indirect comparison.
**Results:** Median progression-free survival (PFS) was 22.1 and 13.3 months for selpercatinib and pralsetinib, respectively (HR = 0.67; 95% CI, 0.53–0.85). Objective response rate was 64.5% and 65.8%, and disease control rate was 92.1% and 90.4%, respectively. Median overall survival was not reached for selpercatinib and 43.9 months for pralsetinib (HR = 0.81; 95% CI, 0.60–1.09). Grade ≥ 3 treatment-related adverse events (TRAEs) were reported in 39.3% and 62.6% of patients, with discontinuations due to TRAEs in 3.6% and 10.0% of patients, respectively.
**Conclusion:** Outcomes were similar; however, PFS was significantly prolonged with selpercatinib, with fewer grade ≥ 3 TRAEs.

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**KEYWORDS**
NSCLC; matching-adjusted indirect comparison; RET inhibitor; selpercatinib; pralsetinib

## 1. Introduction

Gene fusions of *RET* (rearranged during transfection proto-oncogene), a gene encoding for a receptor tyrosine kinase, are known oncogenic drivers of non–small cell lung cancer (NSCLC) and are found in 1–2% of patients with NSCLC [1–3]. *RET* fusions produce a constitutively active *RET* kinase that further activates cell proliferation and survival pathways that drive carcinogenesis [4]. In recent years, selective *RET* inhibitors selpercatinib and pralsetinib have been developed. The US Food and Drug Administration granted accelerated approval in May 2020 for the use of selpercatinib for patients with *RET* fusion–positive NSCLC, following the results of the LIBRETTO-001 clinical trial [5,6]. The European Medicines Agency granted conditional approval for selpercatinib in February 2021 [7]. Pralsetinib was granted accelerated approval by the US Food and Drug Administration for treatment of *RET*-altered NSCLC in September 2020 and conditional approval by the European Medicines Agency in September 2021 following the results of the ARROW trial [8–10].

Approval of selpercatinib and pralsetinib for treatment of *RET* fusion – positive NSCLC was based on single-arm clinical trials, and no head-to-head randomized comparative trials of these drugs are currently available or ongoing, to the best of our knowledge. It is difficult to compare patient outcomes on two treatment regimens across distinct single-arm trials, as any differences in the treated populations may introduce bias in the data. To circumvent these issues, methods for performing indirect comparisons have been developed in recent years [11,12]; in particular, the National Institute for Health and Care Excellence (NICE) recommends the use of matching-adjusted indirect comparisons (MAICs) to compare the outcomes of single-arm trials by weighting individual patient-level data from the trial where individual patient data are available to aggregate data available from another trial [13,14]. By adjusting for baseline prognostic factors, including demographic and clinical characteristics, trial imbalances in patient characteristics are accounted for and outcomes can be meaningfully compared assuming there are no further imbalances such as unknown or missing data on prognostic effects or socioeconomic differences. Selpercatinib and pralsetinib both being new drugs, healthcare professionals and payers would find comparative efficacy and safety data relevant for decision-making. The aim of the present study was to perform an adjusted indirect comparison between selpercatinib and pralsetinib in patients with advanced *RET* fusion – positive NSCLC.

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Article highlights

**Background:**
- Selpercatinib and pralsetinib are selective RET inhibitors that are approved for the treatment of RET-rearranged non – small cell lung cancer (NSCLC), based on LIBRETTO-001 and ARROW single-arm trials, respectively.
- No head-to-head randomized comparison of these drugs is available.

**Methods:**
- We conducted a matching-adjusted indirect comparison (MAIC) of the NSCLC data from LIBRETTO-001 trial and published data from ARROW trial. Selpercatinib data were weighted to match pralsetinib aggregate baseline characteristics.
- Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were compared at the 5% significance level for the overall population and treatment-naive and platinum-pretreated subgroups using 95% confidence intervals (CIs).
- Treatment-related adverse events (TRAEs) and treatment discontinuations due to TRAEs were compared across the 2 trials.

**Results:**
- In the overall population, after weighting, the median PFS for selpercatinib was 22.1 months (hazard ratio [HR] = 0.67 [95% CI, 0.53–0.85]), while the median PFS for pralsetinib was 13.3 months.
- The median OS, after weighting, for pralsetinib, was 43.9 months, while median OS was not reached for selpercatinib (HR = 0.81 [95% CI, 0.60–1.09]). In the overall population after weighing, the ORR for pralsetinib was 72.4% (95% CI, 63.3–80.3) while the ORR for selpercatinib was 64.5% (95% CI, 60.1–69.1), with an odds ratio (OR) of 0.94 (95% CI, 0.71–1.24).
- After weighing, the DCR overall for pralsetinib was 89.7% (95% CI, 82.6–94.5) while the DCR overall for selpercatinib was 92.1% (95% CI, 89.2–95.2) with an OR of 1.24 (95% CI, 0.76–2.39).
- Overall, 39.3% of patients treated with selpercatinib and 62.6% of patients treated with pralsetinib experienced grade ≥ 3 TRAEs (OR = 0.39 [95% CI, 0.29–0.49]), after weighting. 3.6% of patients treated with selpercatinib and 10.0% of patients treated with pralsetinib discontinued treatment due to TRAEs (OR = 0.34 [95% CI, 0.14–0.58]).

**Conclusions:**
- The DCR and ORR of selpercatinib and pralsetinib were similar; however, PFS was significantly prolonged with selpercatinib in patients previously treated with platinum-based chemotherapy.
- Selpercatinib was associated with fewer grade ≥ 3 TRAEs and treatment discontinuations due to TRAEs.

## 2. Methods

### 2.1. Data sources

Data available for our analyses were individual patient-level data collected up to the June 2021 data cut of the LIBRETTO-001 trial (NCT03157128; dataset owner: Eli Lilly and Company) [6] and published aggregate data from the March 2022 data cut of the ARROW trial (NCT03037385) [10,15]. These trials had very similar designs and inclusion and exclusion criteria and were initiated at about the same time: LIBRETTO-001 in May 2017 and ARROW in March 2017. The LIBRETTO-001 trial was a phase I/II, single-arm, open-label study of selpercatinib in patients with *RET*-altered cancers including *RET* fusion – positive advanced NSCLC conducted at 89 sites in 16 countries [6,16,17]. The ARROW trial was a phasel/II, single-arm, open-label study of pralsetinib in patients with *RET*-altered cancers including *RET* fusion – positive advanced NSCLC conducted at 71 sites in 13 countries [10,15,18]. In both trials, the NSCLC efficacy populations consisted of patients with *RET* fusion-positive NSCLC who had at least 6 months of follow-up prior to cutoff and had not been previously treated with a selective *RET* inhibitor. Also, in both studies patients with NSCLC were stratified for efficacy analysis by line of treatment: they were either "treatment naive" or "pretreated" with platinum-based chemotherapy. Safety was compared using data for all patients who received at least 1 dose of the study drug. The present reanalysis of previously published data falls within the scope of the original study approvals.

### 2.2. Patient characteristics

Patient characteristics were selected for weighting in the MAIC based on a systematic literature review (SLR) conducted on prognostic characteristics in NSCLC. Data on prognostic and predictive factors were abstracted from studies of patients with disease progression published since 2010. The selection was limited by availability of baseline characteristics in both trials, and by what was reported in the most recent ARROW publication. However, most characteristics identified in the SLR and relevant for patients with *RET* alterations were available for weighting, including age (the percentage of patients aged 65 years or older) [19–32], sex [21,23–26,33–40], race (percentage of Asian vs. non-Asian participants) [33], smoking status (ex-smoker or current smoker vs never smoker) [27–30,35–37,41–53], Eastern Cooperative Oncology Group (ECOG) performance status (ECOG score of 0–1 vs 2) [22,23,26–29,34,35,37,38,41–43,47,49–51,54–75], presence of brain metastases at baseline [29,47,68–70,76,77], prior use of platinum chemotherapy [25,27,49,51,78], prior immune checkpoint inhibitor use [33,79], and prior multikinase inhibitor (MKI) use [31,34,42,46,71,80]. Specific fusion partners (*KIF5B* [kinesin family 5B gene] and *CCDC6* [coiled-coil domain containing 6 gene]) were also used to weight data in the overall efficacy and safety populations. The MAIC can reliably adjust for confounding due to differences in trial populations only if all important prognostic factors are available from both trials and included in the analysis [81]. Therefore, to check this assumption, all covariates of interest available in LIBRETTO-001 were investigated for possible prognostic effects on overall survival (OS) and progression-free survival (PFS) in a random forest model and Cox model. Time since diagnosis had been reported as being an important prognostic factor in the literature and was found to be significant in the LIBRETTO-001 data for PFS, but it was not reported in the ARROW publications used in the current analysis. Therefore, sensitivity analyses were conducted for time since diagnosis by imputing values based on the distribution of this variable in the LIBRETTO-001 data.

### 2.3. Outcomes

Treatment outcomes compared included the objective response rate (ORR), disease control rate (DCR), PFS, and OS from the LIBRETTO-001 and ARROW trials. The definitions of these outcomes are similar between the 2 studies, both of which had ORR as the primary outcome measure. ORR is defined as the proportion of patients with complete or partial response to therapy. DCR is the proportion of patients with complete response, partial response, or stable disease as the best response to therapy. Response and progression status assessed by independent review committee in both trials.

Safety outcomes included treatment-related adverse events (TRAEs) and treatment discontinuation due to TRAEs.

### 2.4. Statistical analyses

#### 2.4.1. MAIC

Individual patient data from the LIBRETTO-001 trial and aggregate data from the ARROW trial were used to perform the matching-adjusted indirect comparison. Because only aggregate data was available from the ARROW trial, LIBRETTO-001 trial data were weighted to match the ARROW trial population characteristics (based on means, standard deviations, and ratios). For each patient in LIBRETTO-001, a weight was calculated on the basis of the patient's baseline characteristics and odds of having been enrolled in the ARROW trial [13]. The outcomes data for each LIBRETTO-001 patient were reweighted based on the estimated weight. Where weights higher than 2 were calculated, sensitivity analyses were performed to assess the effect of giving too much weight to a few patients by trimming their weights and hence limiting the contribution to the outcomes at 2. To evaluate the impact of reweighting on the sample size, the effective sample size was calculated. The *effective sample size* is the number of independent nonweighted individuals that would be required to give an estimate with the same precision as the weighted sample and is calculated as the sum of the rescaled weights, where the rescaling factor corresponds to the average of the weights. To assess how well matching works in reducing the difference between characteristics in the 2 studies, the standardized mean difference was plotted by calculating the difference between the means in each of the baseline characteristics before and after weighting and dividing by the standard deviation. Variance ratio plots were created to visualize the balancing of the variability in patient characteristic data before and after weighting. Analyses were performed in R using code adapted from Phillippo et al. [13,14] to fit unanchored MAICs.

#### 2.4.2. Comparison of outcomes

Time to event outcomes, including PFS and OS, between treatments, were compared by reconstructing individual patient-level survival data from the published Kaplan-Meier curves for PFS and OS from ARROW using the method described by Guyot et al [82]. Kaplan-Meier estimates for selpercatinib were generated from the weighted LIBRETTO-001 patient-level data. Medians, hazard ratios (HRs), and 95% confidence intervals (CIs) were also calculated.

For ORR, DCR, and adverse events, the number of events and odds ratios (ORs) were calculated. For summaries based on matched data, 95% CIs were estimated using bootstrapping. For all outcomes, pralsetinib was treated as the reference population.

#### 2.4.3. Multiple imputation marginalization

Recently, a Bayesian model to perform multiple imputation marginalization (MIM) has been developed as an additional method for comparing outcomes across trials, adjusting for differences in patient characteristics [83]. Multiple imputation marginalization was performed as a sensitivity analysis for PFS and OS outcomes within the overall populations to provide additional information to supplement the MAIC approach [83]. Multiple imputation marginalization offers a method for matching on ARROW baseline characteristics and incorporates correlation structure among these characteristics, as observed in LIBRETTO-001. This adds computational complexity and might more closely reflect the data structure. A novel adaptation of MIM was used to extend this method into a frequentist setting, which included fitting a range of parametric models that used an ensemble (model averaging [84]) of predictions. First, a range of parametric survival models with covariates for the baseline characteristics data was fitted to the LIBRETTO-001 data, and model parameters from these models were simulated using the covariance matrix and point estimates. Covariate data for LIBRETTO-001, with the sample size in LIBRETTO-001, that matched the ARROW summary trial population baseline characteristics were then simulated assuming a mixed multivariate distribution based on the correlation matrix from the LIBRETTO-001 covariate data and the summary covariate data from ARROW. Survival data (time to event) were simulated on the basis of the simulated survival parameters and the imputed covariate data for each parametric model. The simulated time-to-event data for LIBRETTO-001 were censored by sampling from the censoring information in LIBRETTO-001. Marginal Cox models were then fitted to the simulated survival data from LIBRETTO-001 and the reconstructed patient-level survival data from ARROW to produce HRs based only on treatment as a covariate and Kaplan-Meier – type estimates based on models stratified by treatment. Ensembles of the predictions were estimated by taking predictions from each parametric survival model in proportion to their probability of being the best-fitting model. This approach created 3 ensembles, 1 based on Akaike information criterion (AIC) weights, 1 based on Bayesian information criterion (BIC) weights, and 1 based on the mean AIC and BIC weights. Analyses were performed in R. The SimMultiCorrData package [85] was used to simulate a mixed multivariate distribution, and the "simsurv" R package [86] was used to simulate survival data.

## 3. Results

### 3.1. Baseline characteristics

Baseline characteristics of the efficacy populations of selpercatinib-treated and pralsetinib-treated patients with NSCLC are presented in Table 1. Overall, baseline characteristics were similar for the selpercatinib and pralsetinib patient populations prior to weighting. However, the percentage of treatment-naive Asian participants treated with pralsetinib was notably higher (44.8%) than those treated with selpercatinib (18.8%). Median follow-up duration in both trials at the time of data locks was similar at 26.8 months for ARROW and 27.1 months for LIBRETTO-001 [15].

### 3.2. Importance of covariates

The results from the Cox models and random forest indicated that presence of brain metastases at baseline, *KIF5B* mutation,

Table 1. Baseline characteristics of LIBRETTO-001 and ARROW NSCLC Populations.

| | Overall | | | TN | | | PP | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Selpercatinib | | | Selpercatinib | | | Selpercatinib | |
| Characteristic | Pralsetinib (*N* = 281) n (%) | Before weighting (*N* = 355), n (%) | After weighting (*N* = 247[a]), % | Pralsetinib (*N* = 116), n (%) | Before weighting (*N* = 69), n (%) | After weighting (*N* = 37[a]), % | Pralsetinib (*N* = 141), n (%) | Before weighting (*N* = 247), n (%) | After weighting (*N* = 193[a]), % |
| Age, < 65 years | 176 (62.6) | 226 (63.7) | 62.6 | 67 (57.8) | 38 (55.1) | 57.8 | 93 (66.0) | 160 (64.8) | 66.0 |
| Sex, female | 152 (54.1) | 203 (57.2) | 54.1 | 61 (52.6) | 43 (62.3) | 52.6 | 74 (52.5) | 140 (56.7) | 52.5 |
| Race, Asian | 128 (45.6) | 152 (42.8) | 45.6 | 52 (44.8) | 13 (18.8) | 44.8 | 71 (50.4) | 118 (47.8) | 50.4 |
| Smoking history, never smoked | 176 (62.6) | 241 (67.9) | 62.6 | 68 (58.6) | 48 (69.6) | 58.6 | 89 (63.1) | 165 (66.8) | 63.1 |
| ECOG PS | | | | | | | | | |
| 0 | 83 (29.5) | 131 (36.9) | 36.8 | 35 (30.2) | 25 (36.2) | 39.1 | 37 (26.2) | 90 (36.4) | 37.3 |
| 1 | 191 (68.0) | 212 (59.7) | 61.1 | 80 (69.0) | 40 (58.0) | 60.0 | 98 (69.5) | 150 (60.7) | 59.2 |
| 2 | 6 (2.1) | 12 (3.4) | 2.1 | 1 (0.9) | 4 (5.8) | 0.9 | 5 (3.5) | 7 (2.8) | 3.5 |
| Brain metastases at baseline | 97 (34.5) | 106 (29.9) | 34.5 | 34 (29.3) | 16 (23.2) | 29.3 | 55 (39.0) | 77 (31.2) | 39.0 |
| *RET* fusion partner *KIF5B*, yes | 197 (70.1) | 227 (63.9) | 70.1 | 81 (69.8) | 48 (69.6) | 69.8 | 98 (69.5) | 153 (61.9) | 69.5 |
| *RET* fusion partner *CCDC6*, yes | 50 (17.8) | 71 (20.0) | 17.8 | 19 (16.4) | 10 (14.5) | 16.4 | 27 (19.1) | 53 (21.5) | 19.1 |
| Prior ICI | 73 (26.0) | 166 (46.8) | 26.0 | 0 (0) | 0 (0) | 0 | 57 (40.4) | 144 (58.3) | 40.4 |
| Prior MKI use | 45 (16.0) | 98 (27.6) | 16.0 | 0 (0) | 0 (0) | 0 | 39 (27.7) | 85 (34.4) | 27.7 |
| Prior platinum-based therapy | 141 (50.2) | 247 (69.6) | 50.2 | 0 (0) | 0 (0) | 0 | 141 (100) | 247 (100) | 100 |
| Log TSD (months), mean (SD) | NR | 2.6 (1.3) | NE | NR | 0.7 (0.6) | NE | NR | 3.1 (1.0) | NE |
| Lower quartile SA: Log TSD (months), mean (SD) | 1.5 (1.3)[b] | 2.6 (1.3) | 1.5 (1.0) | 0.5 (0.6)[b] | 0.7 (0.6) | 0.5 (0.4) | 2.4 (1.0)[b] | 3.1 (1.0) | 2.4 (0.8) |
| Upper quartile SA: Log TSD (months), mean (SD) | 3.7 (1.3)[b] | 2.6 (1.3) | 3.7 (0.7) | 0.9 (0.6)[b] | 0.7 (0.6) | 0.9 (0.5) | 3.8 (1.0)[b] | 3.1 (1.0) | 3.8 (0.7) |

*CCDC6* = coiled-coil domain containing 6 gene; ECOG PS = Eastern Cooperative Oncology Group performance status; ICI = immune checkpoint inhibitor; *KIF5B* = kinesin family 5B gene; MKI = multikinase inhibitor; NE = not estimable; NR = not reported; NSCLC = non – small cell lung cancer; PP = platinum pretreated; *RET* = rearranged during transfection proto-oncogene; SA = sensitivity analysis; TN = treatment naive, TSD = time since diagnosis.
[a]Effective sample size after weighting. [b]Imputed based on distributions in the data from LIBRETTO-001.
Note: Pralsetinib data were not weighted; trial results are shown in the "after weighting" columns to aid comparison with results for selpercatinib after weighting.

shorter time since diagnosis, and ECOG performance status of 2 versus 0–1 were associated with poorer survival in LIBRETTO-001 (Table S-1, Figures S-1 to S-4). As time since diagnosis was reported in LIBRETTO-001 but not in ARROW, sensitivity analyses were conducted for this variable.

### 3.3. Weighting trial data

The distribution of weights for the overall cohort and the treatment-naive and platinum-pretreated subgroups is presented in Figure S-5 of the Supplementary Material. No extreme weights of 10 or higher were observed in any of the analysis subgroups. Only a few patients had weights of above 2 in each of the subgroups. Baseline characteristics of the LIBRETTO-001 trial populations after weighting are compared with those of the ARROW populations in Table 1. The distribution of baseline characteristics was balanced after weighting across all weighted variables, as shown by the standardized differences plots and variance ratio plots in Figure S-6 to S-8 (Supplementary Material). Weighting reduced the effective sample size of the LIBRETTO-001 population from 355 to 247. This change was particularly noticeable in the treatment-naive group, which was already small before weighting; after weighting, there were 37 treatment-naive patients in the LIBRETTO-001 effective sample.

### 3.4. Survival outcomes

Efficacy outcomes of selpercatinib and pralsetinib are summarized in Table 2. In the overall population, the median PFS for selpercatinib was 22.3 months (95% CI, 19.3–30.4; HR = 0.65 [95% CI, 0.53–0.81]) before weighting and 22.1 months (95% CI, 19.2–30.4; HR = 0.67 [95% CI, 0.53–0.85]) after weighting, whereas the median PFS for pralsetinib was 13.3 months (95% CI, 11.0–16.4) (Figure 1(a)). In the overall population, median OS was not reached for selpercatinib before or after weighting: HR = 0.78 (95% CI, 0.60–1.03) and HR = 0.81 (95% CI, 0.60–1.09), respectively, while the median OS for pralsetinib was 43.9 months (95% CI, 31.2-not reached [NR]) (Figure 1(b)).

In treatment-naive patients before weighting, the median PFS for selpercatinib was 21.9 months (95% CI, 13.8-NR; HR = 0.68 [95% CI, 0.40–1.17]), and after weighting the median PFS was 21.9 months (95% CI, 11.5-NR; HR = 0.83 [95% CI, 0.45–1.52]) (Table 2; Figure 1(c)). The median PFS for pralsetinib in treatment-naive patients was 13.0 months (95% CI, 9.0-NR). Before weighting, the median OS for selpercatinib was not reached (HR = 0.79 [95% CI, 0.46–1.37]), and after weighting, the median OS was 32.3 months (95% CI, 18.5-NR; HR = 1.20 [95% CI, 0.69–2.09]). Median OS was not reached for pralsetinib in this subgroup (Figure 1(d)).

In platinum-pretreated patients, the median PFS for selpercatinib before weighting was 24.9 months (95% CI, 19.3-NR; HR = 0.64 [95% CI, 0.47–0.88]). The median PFS after weighting was also 24.9 months (95% CI, NR-NR; HR = 0.63 [95% CI, 0.45–0.87]). The median PFS for pralsetinib was 16.5 months (95% CI, 9.3–24.2) (Figure 1(e)). The median OS for selpercatinib was not reached before or after weighting (before weighting, HR = 0.66 [95% CI, 0.47–0.93]; after weighting, HR = 0.68 [95% CI, 0.48–0.97]). The median OS for pralsetinib in pretreated patients was 44.3 months (95% CI, 25.0-NR) (Figure 1(f)).

Table 2. Comparison of response and survival outcomes with pralsetinib and selpercatinib.

| | Overall | | | TN | | | PP | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Selpercatinib | | | Selpercatinib | | | Selpercatinib | |
| Study measure | Pralsetinib ($N = 281$) | Before weighting ($N = 355$) | After weighting ($N = 247$[a]) | Pralsetinib ($N = 116$) | Before weighting ($N = 69$) | After weighting ($N = 37$[a]) | Pralsetinib ($N = 141$) | Before weighting ($N = 247$) | After weighting ($N = 193$[a]) |
| ORR, % (95% CI) | 65.8 (60.0–71.4) | 63.7 (58.4–68.7) | 64.5 (60.1–69.1) | 72.4 (63.3–80.3) | 84.1) (73.3–91.8) | 77.1 (67.4–90.1) | 59.6 (51.0–67.7) | 61.1 (54.7–67.2) | 59.2 (53.5–64.7) |
| OR (95% CI) | ref | 0.91 (0.65–1.26) | 0.94 (0.71–1.24) | ref | 2.01 (0.94–4.31) | 1.29 (0.67–4.06) | ref | 1.07 (0.70–1.63) | 0.98 (0.70–1.43) |
| DCR, % (95% CI) | 90.4 (86.3–93.6) | 93.2 (90.1–95.6) | 92.1 (89.2–95.2) | 89.7 (82.6–94.5) | 92.8 (83.9–97.6) | 85.8 (77.0–98.2) | 90.8 (84.7–95.0) | 93.9 (90.2–96.6) | 94.7 (92.7–97.0) |
| OR (95% CI) | ref | 1.47 (0.83–2.60) | 1.24 (0.76–2.39) | ref | 1.48 (0.50–4.39) | 0.70 (0.28–6.45) | ref | 1.57 (0.72–3.40) | 1.83 (0.95–3.58) |
| PFS | | | | | | | | | |
| Median (95% CI), mo | 13.3 (11.0–16.4) | 22.3 (19.3–30.4) | 22.1 (19.2–30.4) | 13.0 (9.0-NR) | 21.9 (13.8-NR) | 21.9 (11.5-NR) | 16.5 (9.3–24.2) | 24.9 (19.3-NR) | 24.9 (NR-NR) |
| HR (95% CI) | ref | 0.65 (0.53–0.81)* | 0.67 (0.53–0.85)* | ref | 0.68 (0.40–1.17)* | 0.83 (0.45–1.52) | ref | 0.64 (0.47–0.88)* | 0.63 (0.45–0.87)* |
| OS | | | | | | | | | |
| Median (95% CI), mo | 43.9 (31.2-NR) | NR (33.5-NR) | NR (30.5-NR) | NR (31.9-NR) | NR (27.9-NR) | 32.3 (18.5-NR) | 44.3 (25.0-NR) | NR (33.5-NR) | NR (30.3-NR) |
| HR (95% CI) | ref | 0.78 (0.60–1.03) | 0.81 (0.60–1.09) | ref | 0.79 (0.46–1.37) | 1.20 (0.69–2.09) | ref | 0.66 (0.47–0.93)* | 0.68 (0.48–0.97)* |

CI = confidence interval; DCR = disease control rate; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; NR = not reached; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PP = platinum pretreated; ref = treatment used as the reference; TN = treatment naive.

*Statistically significant at 0.05 level.

Note: Pralsetinib data were not weighted; trial results are shown in the "after weighting" columns to aid comparison with results for selpercatinib after weighting.

[a]Effective sample size after weighting.

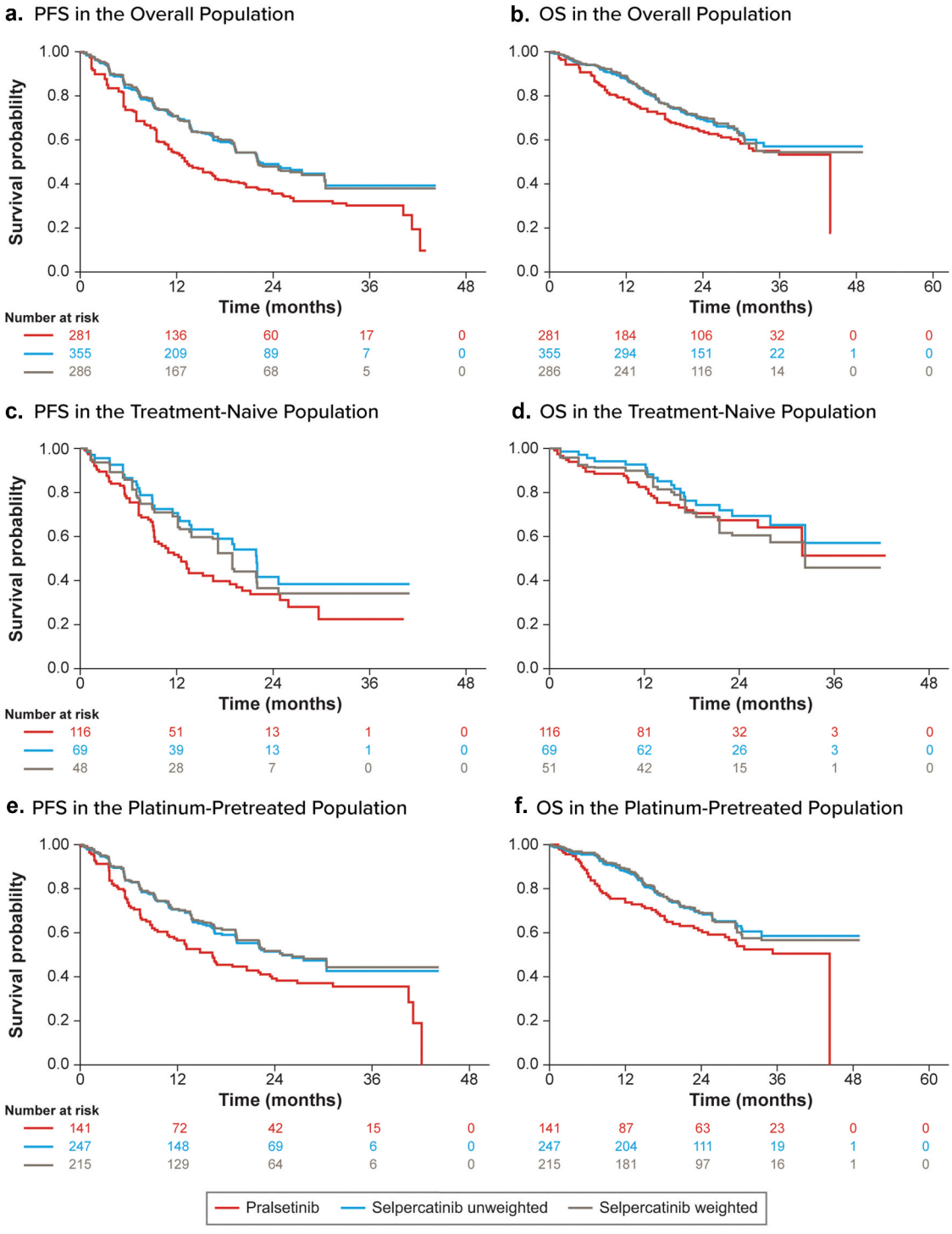


Figure 1. PFS and OS estimated by matching-adjusted indirect comparison.

a. PFS in the Overall Population.

b. OS in the Overall Population.

c. PFS in the Treatment-Naive Population.

d. OS in the Treatment-Naive Population.

e. PFS in the Platinum-Pretreated Population.

f. OS in the Platinum-Pretreated Population.

OS = overall survival; PFS = progression-free survival.

### 3.5. Response to treatment

The ORR and DCR were similar between treatments after weighting (Table 2). In the overall population, the ORR for selpercatinib before weighting was 63.7% (OR = 0.91 [95% CI, 0.65–1.26]), while the ORR for selpercatinib after weighting was 64.5% (OR = 0.94 [95% CI, 0.71–1.24]). The ORR for pralsetinib in the overall population was 65.8%. The DCR for selpercatinib in the overall population before weighting was 93.2% (OR = 1.47 [95% CI, 0.83–2.60]), and the DCR after weighting was 92.1% (OR = 1.24 [95% CI, 0.76–2.39]). The DCR for pralsetinib in the overall population was 90.4%.

In treatment-naive patients after weighting, the ORR for selpercatinib was 77.1% (OR = 1.29 [95% CI, 0.67–4.06]). The ORR for pralsetinib in treatment-naive patients was 72.4%. The DCR in treatment-naive patients was 85.8% for selpercatinib after weighting and 89.7% for pralsetinib (OR = 0.70 [95% CI, 0.28–6.45]).

In platinum-pretreated patients, the ORR was 61.1% for selpercatinib before weighting, 59.2% for selpercatinib after weighting, and 59.6% for pralsetinib in the MAIC (OR = 0.98; 95% CI, 0.70–1.43). In platinum-pretreated patients, the DCR was 94.7% for selpercatinib after weighting and 90.8% for pralsetinib (OR = 1.83 [95% CI, 0.95–3.58]).

### 3.6. TRAEs

Safety analyses were performed using all patients who received at least 1 dose of the study drug for both trials (NSCLC safety population). More detailed information on adverse events associated with selpercatinib and pralsetinib can be found in the original publications of the LIBRETTO-001 and ARROW trials [6,10,15]. There were 356 patients in the selpercatinib-treated safety population before weighting and 247 patients in the safety population after weighting; 281 patients were treated with pralsetinib (Table 3). Before weighting, 40.2% of patients treated with selpercatinib reported grade ≥ 3 TRAEs, compared to 62.6% of patients treated with pralsetinib (OR = 0.40; 95% CI, 0.29–0.55). After weighting, the rate of grade ≥ 3 TRAEs was 39.3% for patients treated with selpercatinib, compared to 62.6% of patients treated with pralsetinib (OR = 0.39; 95% CI, 0.29–0.49). Before weighting, 3.1% of patients treated with selpercatinib discontinued treatment due to grade ≥ 3 TRAEs, compared to 10.0% of patients treated with pralsetinib (OR = 0.29; 95% CI, 0.14–0.59). After weighting, 3.6% of patients treated with selpercatinib discontinued treatment due to grade ≥ 3 TRAEs, compared to 10.0% of patients treated with pralsetinib (OR = 0.34; 95% CI, 0.14–0.58).

### 3.7. Sensitivity analyses

Sensitivity analyses were conducted for the overall, population for MAIC, MAIC with trimmed weights, and MAIC with missing pralsetinib data for time since diagnosis replaced with the lower and upper quartiles from selpercatinib (Table 4). The lower and upper quartiles for the log of time since diagnosis were 1.5 (4.5 months) and 3.7 (40.4 months). Multiple imputation marginalization was also conducted as sensitivity analyses for the overall population and with missing pralsetinib data for time since diagnosis replaced with the lower and upper quartiles from selpercatinib. The lower and upper quartiles for time since diagnosis before and after weighting are presented in Table 1. The results from the sensitivity analyses are included in Table 4. Trimming had little impact on the MAIC results. However, the results did show some sensitivity for the quartiles entered for time since diagnosis. For example, the HRs had ranges of 0.37 to 0.75 for PFS and 0.44 to 0.83 for OS. The results from the MIM were similar to those from MAIC, although they appeared to be less sensitive to the quartiles used for time since diagnosis. The HR calculated for PFS using MIM was 0.63 (95% CI, 0.50–0.78), while the MIM HR for OS was 0.82 (95% CI, 0.63–1.08) (Table 4; Figures S-9 and S-10). For the time since diagnosis quartiles, the HRs from MIM ranged from 0.48 to 0.65 for PFS and 0.68 to 0.90 for OS. However, HRs calculated from the MIM were sensitive to the choice of distribution, with point estimates ranging from 0.53 to 1.05 for PFS and 0.51 to 1.11 for OS (Table S-3).

## 4. Discussion

Our study suggests that while selpercatinib and pralsetinib have similar efficacy across the overall population in terms of the primary efficacy outcome (ORR), selpercatinib seems to have more favorable toxicity profile compared with pralsetinib. In this MAIC analysis, selpercatinib and pralsetinib resulted in similar ORR and DCR in the overall population and across both treatment-naive and platinum-pretreated patient subgroups.

Table 3. Safety comparison for all patients with NSCLC.

| | Pralsetinib NSCLC safety ($N = 281$) | Selpercatinib NSCLC safety, before weighting ($N = 356$) | | Selpercatinib NSCLC safety, after weighting ($N^{eff} = 247$) | |
|---|---|---|---|---|---|
| Binary outcome | Rate, % (95% CI) | Rate, % (95% CI) | OR vs pralsetinib (95% CI) | Rate, % (95% CI) | OR vs pralsetinib (95% CI) |
| Grade ≥3 TRAE | 62.6 (56.7–68.3) | 40.2 (35.0–45.5) | 0.40 (0.29–0.55) | 39.3 (34.8–43.9) | 0.39 (0.29–0.49)* |
| Treatment discontinuation due to TRAEs | 10.0 (6.7–14.1) | 3.1 (1.6–5.5) | 0.29 (0.14–0.59) | 3.6 (1.4–5.4) | 0.34 (0.14–0.58)* |

CI = confidence interval; $N_{eff}$ = effective sample size; NSCLC = non – small cell lung cancer; OR = odds ratio; *RET* = rearranged during transfection proto-oncogene; RD = relative difference; RR = relative risk; TRAE = treatment-related adverse event.
*Statistically significant at the 0.05 level.
Notes: The ARROW trial was used as a reference in the comparison: OR = odds in LIBRETTO-001/odds in Arrow; RR = risk in LIBRETTO-001/risk in Arrow; RD = risk in LIBRETTO-001 - risk in ARROW.

Table 4. Comparison of Selpercatinib vs pralsetinib survival outcomes in primary and sensitivity analyses.

| | Overall NSCLC Population | |
|---|---|---|
| | PFS, HR (95%CI) | OS, HR (95%CI) |
| Primary analysis (MAIC) | 0.67 (0.53–0.85)* | 0.81 (0.60–1.09) |
| Sensitivity analyses | | |
| MAIC, trimmed weights | 0.66 (0.52–0.83)* | 0.79 (0.59–1.06) |
| MAIC, lower quartile for TSD | 0.75 (0.57–0.99)* | 0.83 (0.58–1.19) |
| MAIC, upper quartile for TSD | 0.37 (0.23–0.58)* | 0.44 (0.26–0.74)* |
| MIM | 0.64 (0.51–0.80)* | 0.89 (0.68–1.16) |
| MIM, lower quartile for TSD | 0.65 (0.52–0.81)* | 0.90 (0.69–1.18) |
| MIM, upper quartile for TSD | 0.48 (0.38–0.61) * | 0.68 (0.51–0.90)* |

CI = confidence interval; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; MIM = multiple imputation marginalization; NSCLC = non – small cell lung cancer; OS = overall survival; PFS = progression-free survival; TSD = time since diagnosis.
*Statistically significant at 0.05 level.
Note: MIM data are from an ensemble model using the mean Akaike information criterion and Bayesian information criterion weights.

There may be a PFS benefit to patients treated with selpercatinib in the overall population and in patients previously treated with platinum-based chemotherapy. Selpercatinib resulted in significantly improved PFS in patients who were pretreated with platinum chemotherapy, while in treatment-naive patients, there was no statistically significant difference in PFS estimates between both RET inhibitors after weighting. Consistent results for PFS and OS were found in the sensitivity analyses using an alternative estimation method (MIM) in the overall NSCLC efficacy population. Both comparisons indicated that selpercatinib improved PFS when compared with pralsetinib. For OS, the MAIC and MIM results indicated that OS estimates were not significantly different between both treatment groups when comparing the overall populations. In the NSCLC safety population, patients treated with pralsetinib experienced a higher rate of grade ≥ 3 TRAEs than patients treated with selpercatinib. Patients treated with selpercatinib were also less likely to discontinue therapy due to TRAEs.

Evaluation of *RET* inhibitors to treat *RET* fusion – positive NSCLC is still ongoing. In addition to the single-arm ARROW trial, pralsetinib is being evaluated against standard of care in the phase III AcceleRET trial [87]. Furthermore, the recent LIBRETTO-431 phase III randomized trial demonstrated that selpercatinib treatment leads to significantly longer PFS than the current standard of care (platinum chemotherapy with or without pembrolizumab) in patients with *RET* fusion – positive NSCLC [88]. While research on *RET* inhibitors develops, this study helps fill the gap in comparative data between selpercatinib compared with pralsetinib. Matching-adjusted indirect comparisons have been applied to many classes of drugs, including immunotherapy for first-line treatment of nonsquamous advanced NSCLC [89,90]. As the use of MAIC expands to compare treatments that were approved on the basis of single-arm trials, new studies are ongoing to determine the impact of these comparison studies on health technology assessment (HTA) agency evaluations and decision-making [91–93]. Thus far, many MAIC studies presented to HTA agencies have resulted in recommendations from the HTA agency in question [91,93].

This study offers important patient outcome comparisons for patients with *RET* fusion-positive NSCLC, and both trials had similar designs, including follow-up time, and patient baseline characteristics. However, there were some limitations to the study. The overall survival data were not mature in either trial. In general, the small effective sample size in the MAIC of the treatment-naive selpercatinib subgroup, in part due to the proportion of Asian patients in this population, increased the uncertainty around the estimates of comparative effectiveness in these patients across the outcomes. This was particularly the case for OS results, which were further influenced by uncertainty due to immaturity of the data. The small sample size also impacted the sensitivity analyses conducted for time since diagnosis. However, the MIM was less affected by this issue because the 95% CIs from parametric survival models were more reflective of the total number of patients. Furthermore, both unanchored MAIC and unanchored MIM relied on the same assumption that treatment outcomes can be predicted from baseline covariates; that is, that all treatment effect modifiers and prognostic factors are known, measured, and available for both studies. Prognostic factors, identified in the literature and used to weight the unanchored MAIC, included ECOG performance status, tumor stage, time since diagnosis, age, gender, smoking status, race, and *RET*-alteration status. However, some prognostic factors were identified in the literature that were not reported by both LIBRETTO-001 and ARROW studies. These included weight loss and body mass index [23,32,33,49,63,70,72,94,95], response to previous therapy [27,30,41,48,79,95], epidermal growth factor receptor mutation status [41,47,54,69,74,79,96–98], comorbidities [28,63,75], histology [27,29,32,33,41,68], central nervous system metastases [29,47,68–70,76,77], and Japanese nationality [33]. Since it is never possible to test these assumptions, the amount of bias in these estimates is unknown. The bias may be substantial and could even exceed the magnitude of treatment effects that are being estimated. Additionally, MAIC also assumes overlap between the covariate distributions in both studies. As the degree of overlap is reduced more weight is given to a small number of patients, which may bias results. More specifically, our MAIC assumed that the study population in ARROW was entirely contained within the study population in the LIBRETTO-001 trial. MIM made the same assumptions as MAIC regarding unmeasured covariates but did not assume that the ARROW population was contained in the LIBRETTO-001 population.

## 5. Conclusion

In the overall population and platinum-pretreated subgroup, PFS was significantly improved in patients treated with selpercatinib, though that trend did not extend to OS, where there was no significant difference, according to MAIC analyses. The ORR and DCR with selpercatinib and pralsetinib were similar. Selpercatinib was associated with fewer grade ≥ 3 TRAEs and a lower rate of treatment discontinuations due to TRAEs.

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## Author contributions

Maximilian Hochmair: Writing-review and editing. Urpo Kiiskinen: conceptualization, methodology, resources, writing-review and editing, supervision, project administration, funding acquisition. Yulia Dyachkova: conceptualization, methodology, investigation, writing-review and editing, project administration. Tarun Puri: conceptualization, methodology, resources, writing-review and editing, supervision, project administration, funding acquisition. Xuwen Wang: conceptualizatoin, methodology, investigation, writing-review and editing. Sorrel Wolowacz: conceptualization, methodology, investigation, writing-review and editing, project administration. Adrian Vickers: conceptualization, methodology, investigation, formal analysis, writing-review and editing, project administration. Ernest Nadal: Writing-review and editing.

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## Ethical disclosure statement

Data analysis performed in this study was conducted in line with the LIBRETTO-001 (NCT03157128) clinical trial protocol. The LIBRETTO-001 trial and the ARROW clinical trials were conducted in line with country and local guidelines and the protocols were approved by institutional review boards or ethics committees at each site. All patients (or patient guardians) gave informed consent. Both trials were conducted in accordance with the International Conference on Harmonization for Good Clinical Practice and the Declaration of Helsinki.

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## Data availability statement

Lilly provides access to all individual patient data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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