# External control cohorts for the single-arm LIBRETTO-001 trial of selpercatinib in RET+ NSCLC cancer


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Eli Lilly and the company


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# Outline

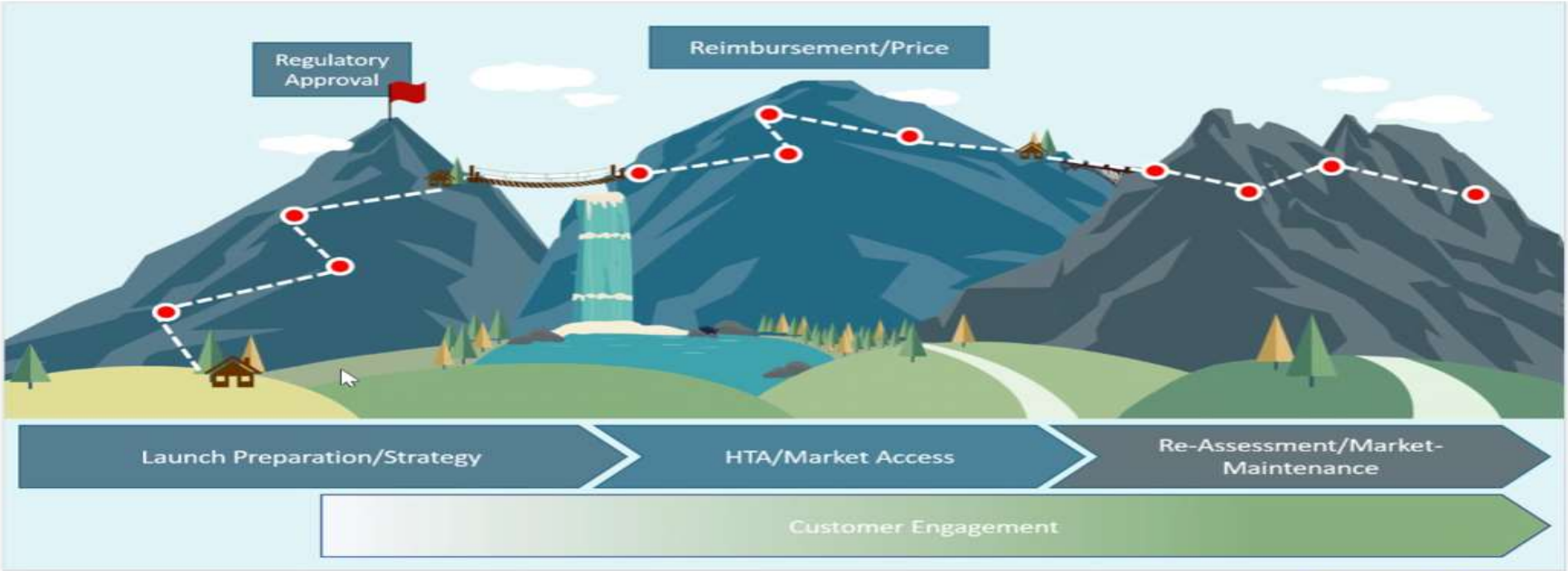
- Setting the themes
  - Background: An evolving paradigm to market access
  - Libretto-001: Selpercatinib in RET-altered cancers
  - Challenge: Evidence gaps inherited from single-arm trials for accelerated access

- Optimized likelihood for accelerated access for patients
  - Mitigated anticipated risks/uncertainties when synthesis evidence to fill the gaps inherited from single arm trial

# An evolving paradigm for market access

**YESTERDAY:** The demonstration of a positive Benefit/Risk profile was usually enough to gain reimbursement

**TODAY:** A novel agent must demonstrate superior medical value and/or cost effectiveness benefits




Slide courtesy of the IBU stats team

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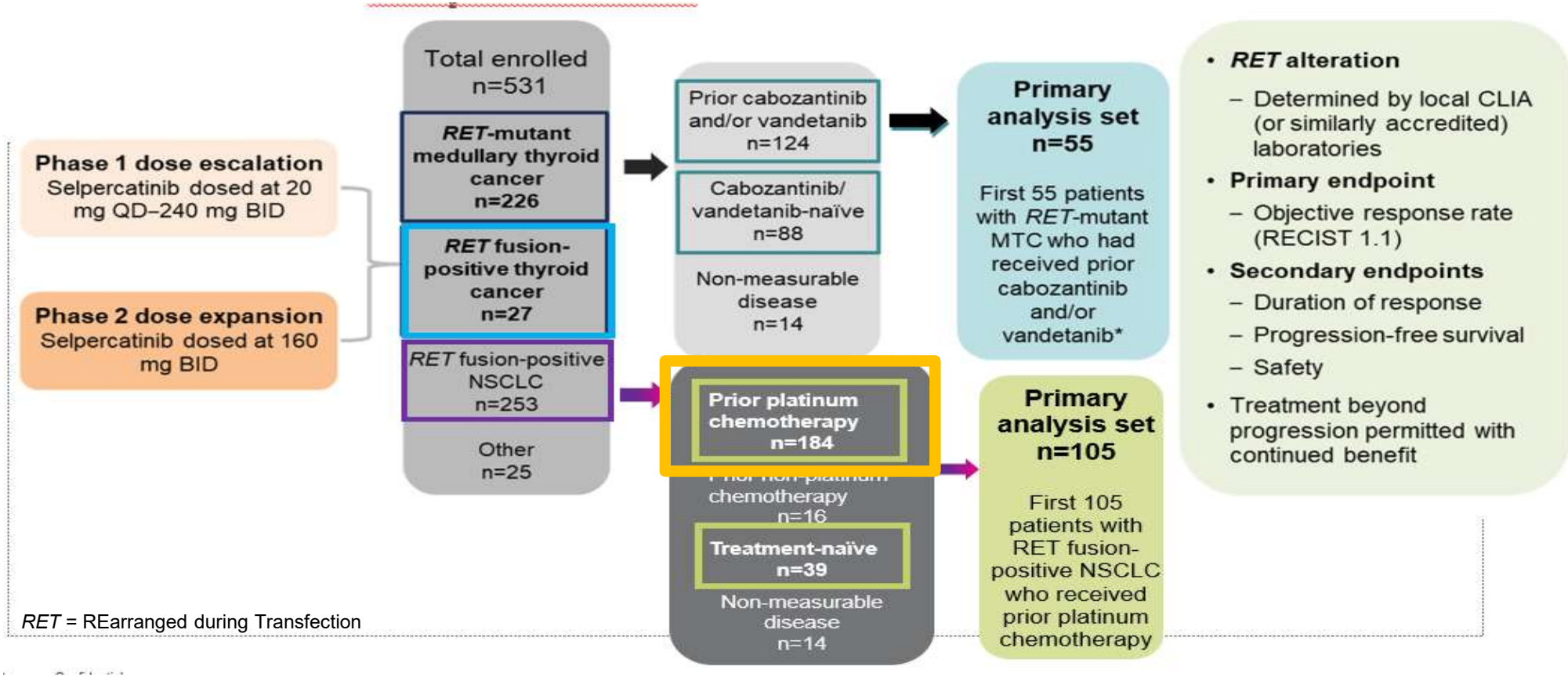
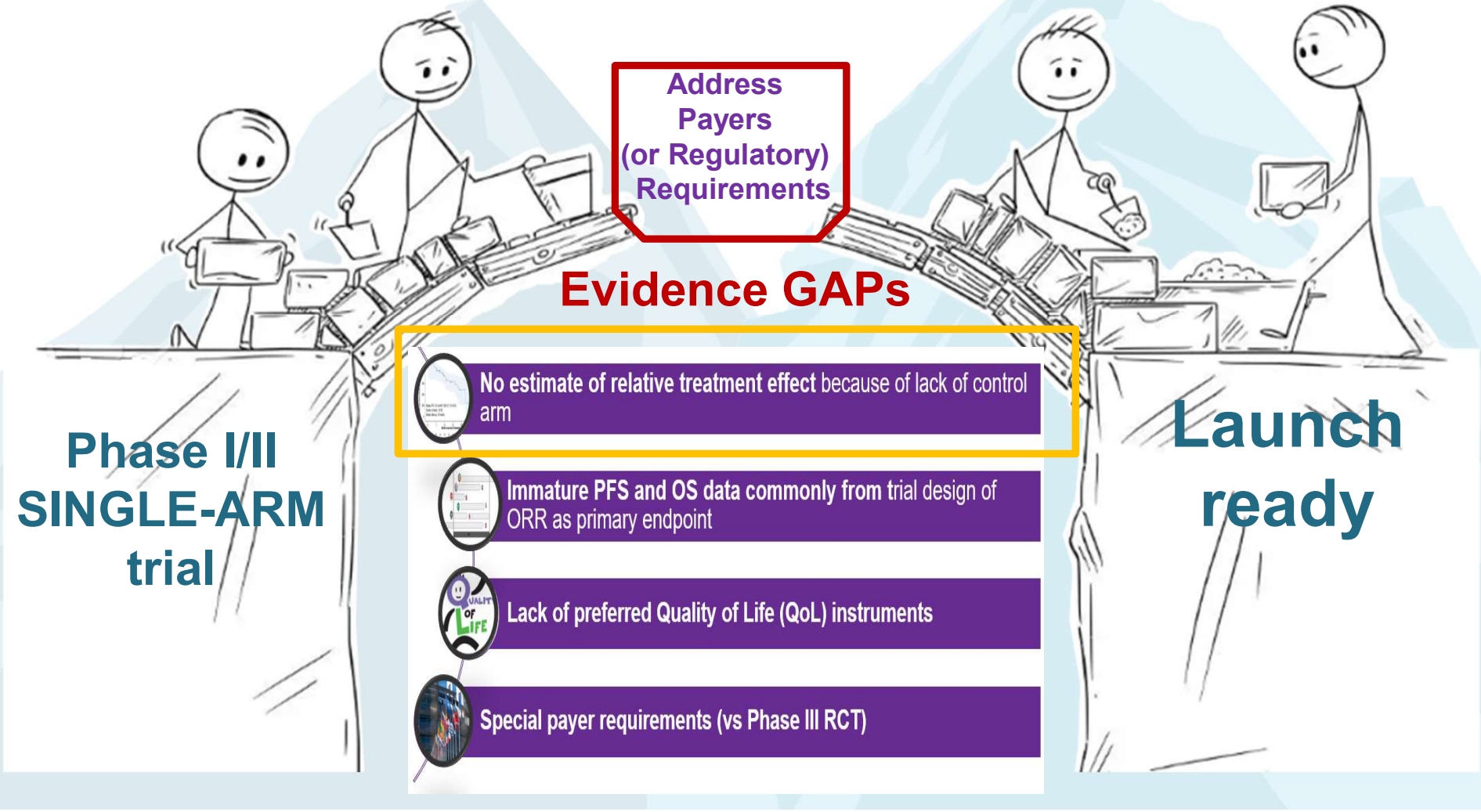
# Libretto-001: Selpercatinib in RET-altered cancers




*RET* = REarranged during Transfection


# ACCELERATE market access via SINGLE-ARM trial (but not RCTs) is getting common

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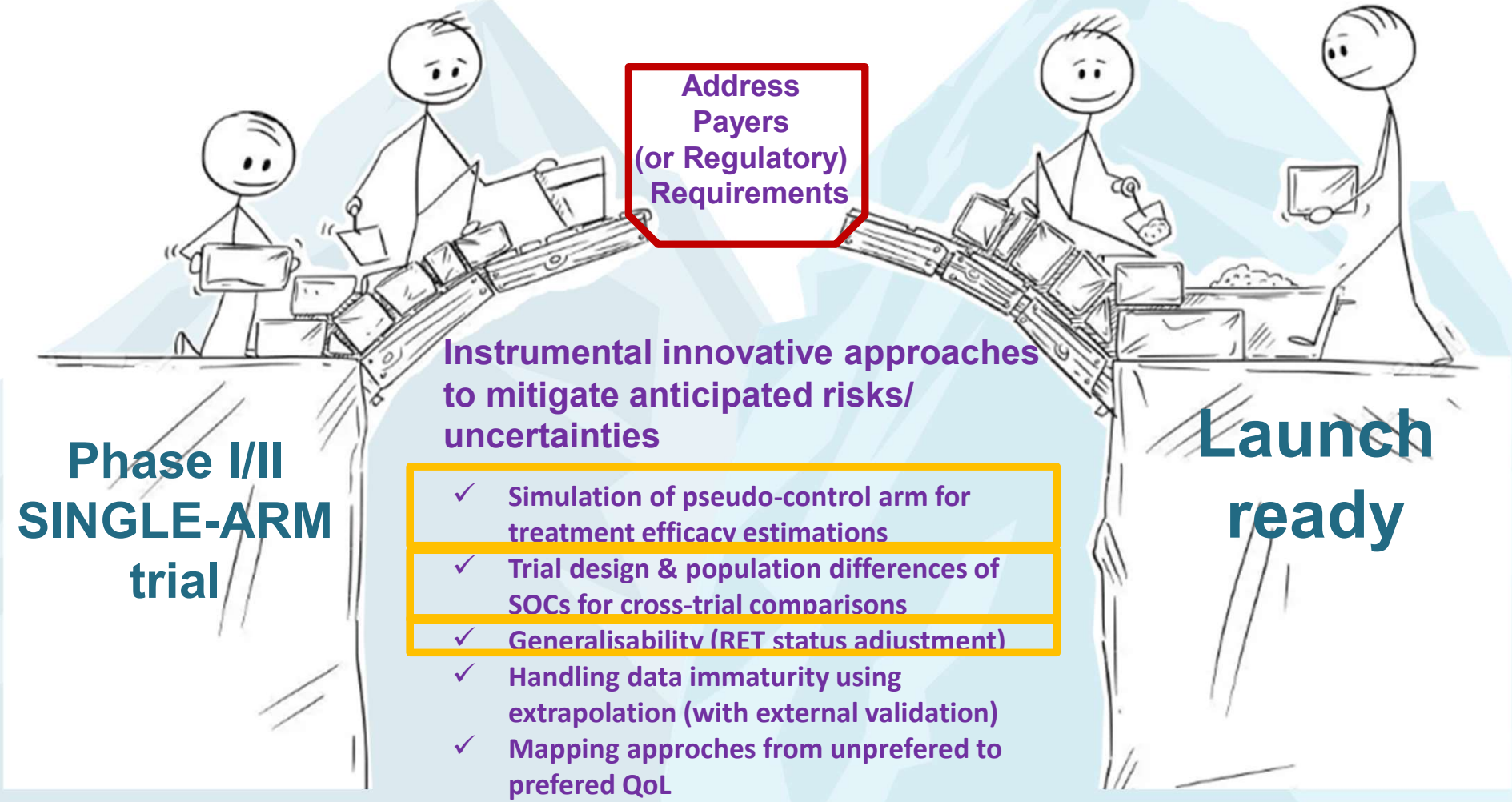


# Optimized likelihood for accelerated access

- Estimating comparative efficacy of selpercatinib versus other available treatments for pre-treated RET+ lung cancer:

- Two-fold approach:
  1) Synthesize external control arm* using
     - ✓ Real-world data
     - ✓ Historical trial data

  2) Compare to standard of care(s) (SOCs) by addressing
     - ✓ Trial design and population differences of SOCs (i.e. biomarkers) cross trials

*Rolfo et al 2022 External control cohorts for the single-arm LIBRETTO-001 trial of selpercatinib in RET+ non-small-cell lung cancer

# Synthesize external control arm

## Part 1: Real-world control

# Objectives

- Compare efficacy (PFS, ORR and OS) of LIBRETTO-001 pre-treated NSCLC cohorts to corresponding real-world (RW) cohorts from Clinico-Genomic Database (CGDB)

- Three analytic approaches:
  - Analytic strategy 1: RET fusion positive control cohorts consistent with LIBRETTO-001
  - Analytic strategy 2: Control cohorts consistent LIBRETTO-001, other than RET status
  - Analytic strategy 3: Apply a factor to account for unknown RET status

- Primary comparison: Blended control

# Eligibility of real-world cohort

- LIBRETTO-001 timeframe: Initiating index line of therapy ≥ May 2017
- No clinical trial enrollment
- No history of RET inhibitor use
- No coexisting alterations (ALK, EGFR, ROS1, KRAS, BRAF)
- *RET* fusion positive

# Possible sources of bias

- Favoring CGDB RW cohorts:
  - ✓ Immortal time bias in CGDB
  - ✓ Fewer patients 3rd line or later
  - ✓ More with earlier disease stage at diagnosis
- Favoring Libretto-001:
  - ✓ Any unique prognostic effect of RET fusion + status
  - ✓ More non-squamous, females and never-smokers
  - ✓ Younger, lower body weight, with better performance status
- Entropy balancing method was used to adjust for measured sources of possible bias.

# Entropy Balancing (EB)

- Unlike propensity scoring methods, EB directly balances the distribution of variables between groups
- May be preferred when samples are small to avoid loss of population size, or when there are prespecified variables for the comparison groups to be balanced
- Results in a perfect match but may result in some extreme weights to achieve this.

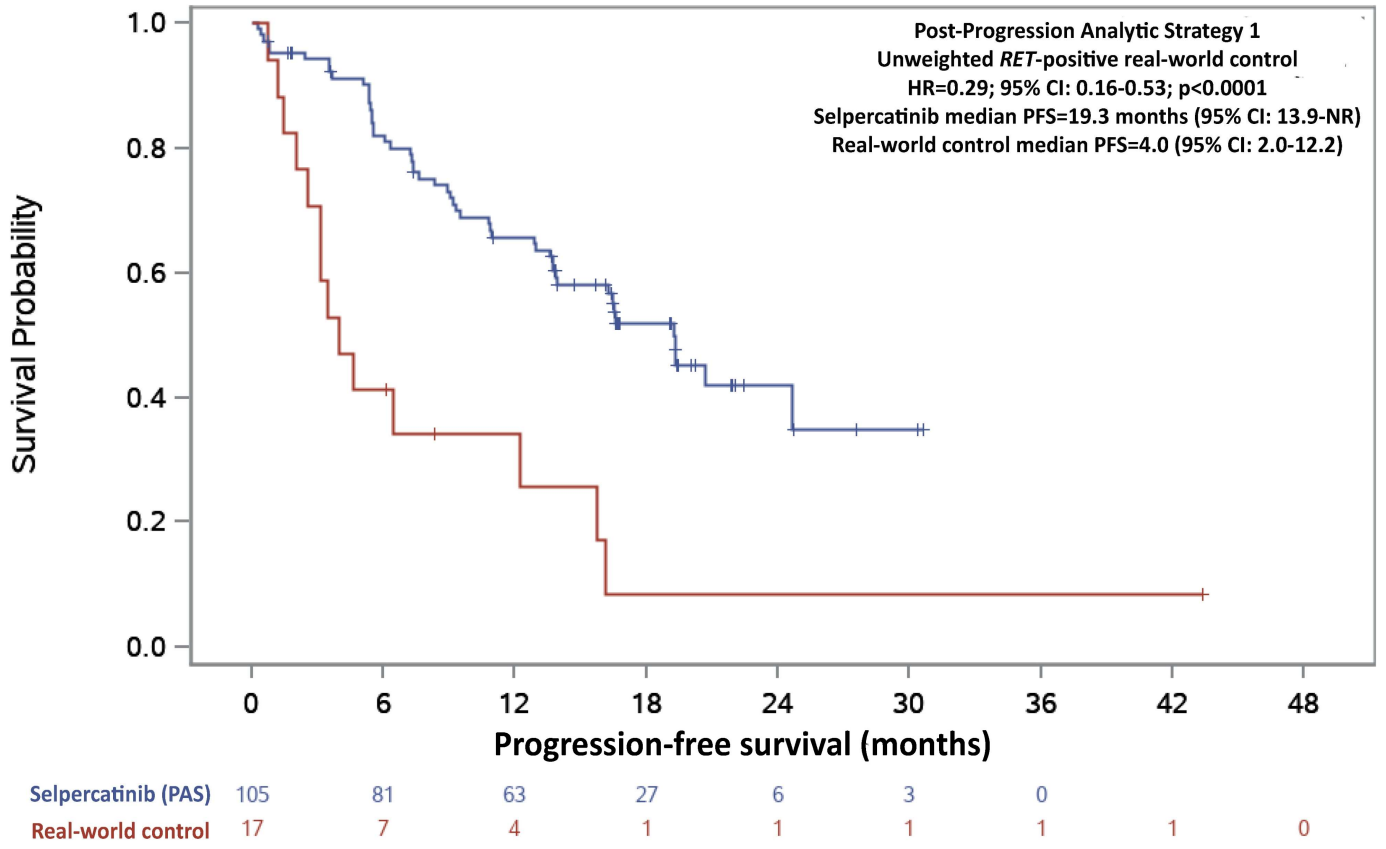
# Covariates for EB

- Systematic literature review:
  - ✓ Sex
  - ✓ Age
  - ✓ Body weight
  - ✓ ECOG performance status
  - ✓ Smoking status
  - ✓ NSCLC Histology
  - ✓ Presence of brain metastasis
  - ✓ Time from advanced/metastatic diagnosis to the start of index therapy
  - ✓ Disease stage at initial diagnosis

# Patients included in analyses

| | Real-world/ post-progression | LIBRETTO-001/ post-progression |
|---|---|---|
| **Analytic strategy 1 (RET+)** | **17** | **105** |
| **Analytic strategy 2 & 3 (Any RET status)** | **1,503** | |

# PFS, post-progression (RET+ cohort)

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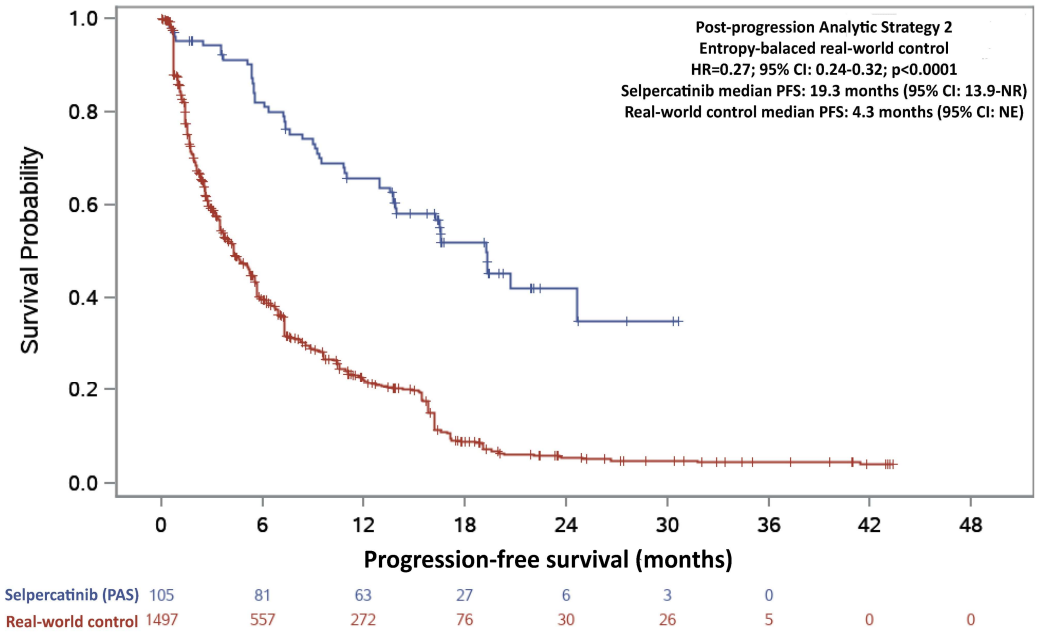
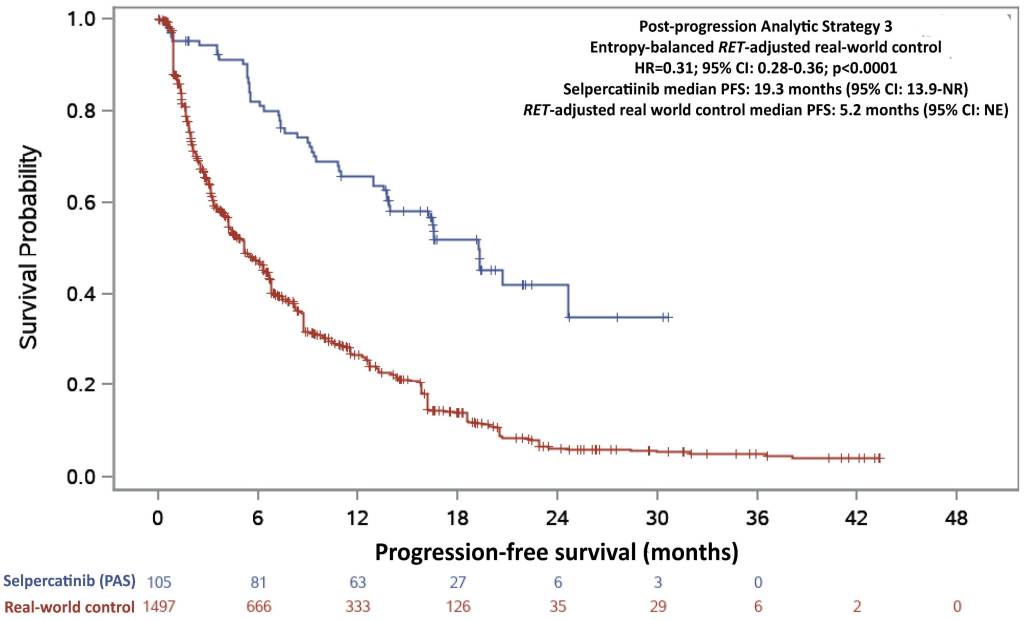
# PFS, post-progression (all patients)

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# Synthesize external control arm

## Part 2: Historical trial control

# Objectives

- Compare efficacy (PFS and OS) of LIBRETTO-001 pre-treated NSCLC cohorts to relevant SOCs
  - ✓ Generalisability (i.e RET status adjustment)
  - ✓ Synthesize external control arm (used REVEL trial )
  - ✓ Compare to standard of care(s)

# High level summary of the approaches

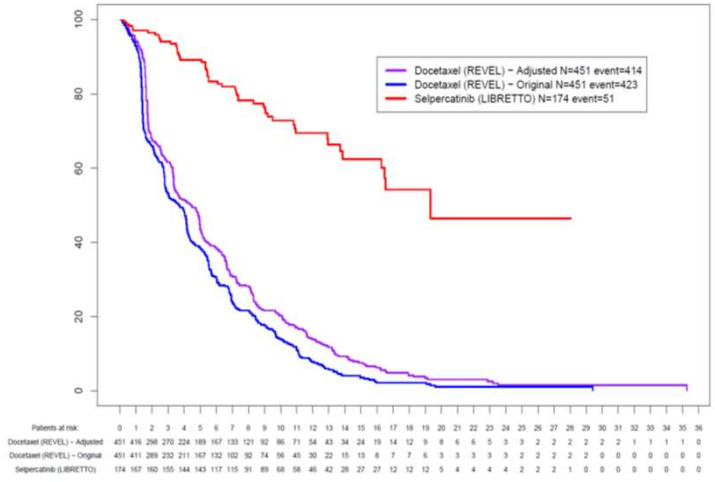
- Generalisability
  - ✓ Utilise Flatiron CGDB data to provide an estimate of a **time acceleration factor** for RET+, using multivariable statistical techniques.
  - ✓ Utilise the time acceleration factor to adjust the historical trial data
- Synthesize external control arm
  - ✓ Fit models to the adjusted historical trial data combined with the LIBRETTO-001 data to estimate an adjusted data set matched to the LIBRETTO-001 study
- Compare to standard of care(s)
  - ✓ Trial design and population differences of SOCs (i.e. biomarkers) cross trials via a hybrid Bayesian NMA approach

# Adjusted historical trial data to reflect a RET+ population

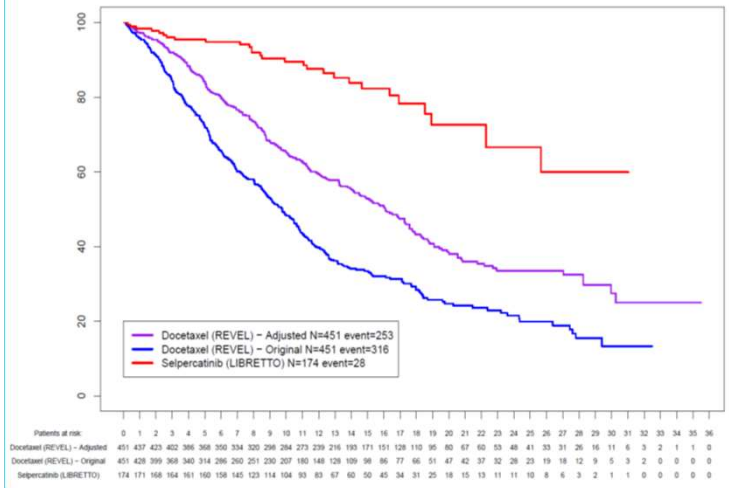
- Estimated effect of RET-fusion status of RET+ vs RET- on PFS and OS from Flatiron data

| Survival model | Post-progression PFS | Post-progression OS |
|---|---|---|
| Time acceleration factor | 1.2 | 1.65 |

PFS




OS



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# Summary of Patient Characteristics of the REVEL and LIBRETTO Trial Populations

| Characteristic | REVEL (n = 625) | LIBRETTO PAS (n = 105) | LIBRETTO IAS (n = 184) |
|---|---|---|---|
| Age (median) | 62 | 61 | 62 |
| Female | 33.6% | 59.0% | 57.1% |
| Race: White | 80.5% | 52.4% | 46.7% |
| Race: Asian | 13.8% | 38.1% | 44.6% |
| Race: Other | 5.70% | 9.50% | 8.70% |
| Never smoked | 22.6% | 71.4% | 67.9% |
| Histology: Non-squamous | 71.6% | 100% | 100% |
| ECOG ≥ 1 | 67.9% | 70.5% | 64.2% |
| Prior surgery | 18.1% | 47.6% | 45.7% |
| Stage IV at diagnosis | 81.8% | 96.2% | 92.4% |
| Time since diagnosis to start of trial (median months) | 9.2 | 30.1 | 24.2 |
| Sum of longest diameters of tumours (mm) (median) | 67 | 60.0 | 54.7 |
| ≥ 2 metastatic sites | 86.4% | NR | NR |
| CNS metastases at baseline | 3.8% | 35.2% | 32.6% |

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; IAS = integrated analysis set (all patients treated with platinum-based chemotherapy); NR = not reported; NSCLC = non–small cell lung cancer; PAS = Primary Analysis Set (the first consecutively enrolled patients previously treated with platinum-based chemotherapy).

# Methodologies applied for comparative efficacy estimation

- **Matching methods (Multivariable regression, 1:1 matching ratio)**
  a. Propensity score matching (on logit of the propensity score scale)
  b. Genetic matching (weights assigned to each covariates to find the optimal balance)

- **Propensity score weighting (PSW)**
  a. Based on a generalized boosted model
  (an iterative process with multiple regression trees, $w_i$=1 for Libretto-001 cohort and $w_i = p_i/(1-p_i)$ for REVEL cohort)
  b. Based on a logistic regression model ($w_i=p_i$ for REVEL cohort)

- **Doubly robust - targeted minimum loss-based estimation (TMLE)**

# Baseline characteristics of patients treated with selpercatinib and clinical trial controls, before and after matching

| 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) $n = 218$[a,b] | 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 $\leq 1$, % | 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 |

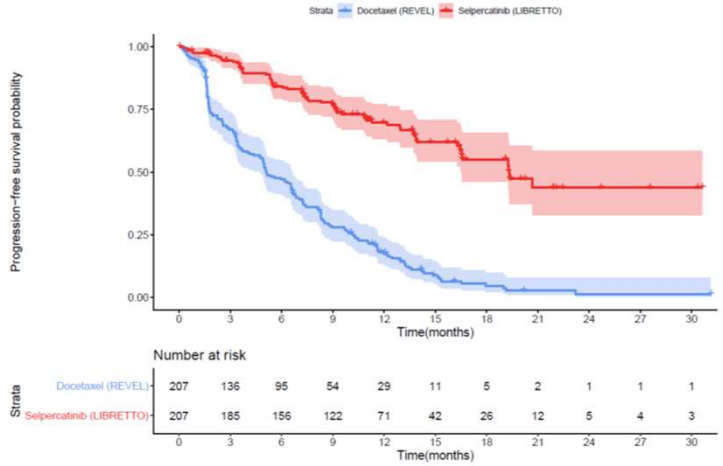
ECOG PS, Eastern Cooperative Oncology Group performance status; PSW, propensity score weighting.

[a]Four patients without non-squamous histology were excluded from further matching process.

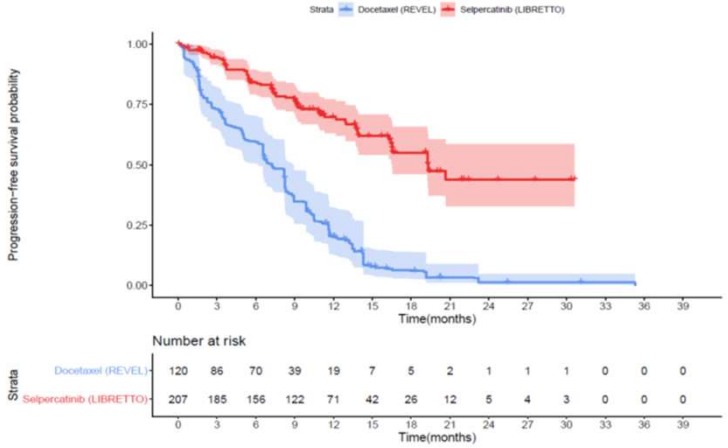
[b]Five patients with ECOG PS $\geq 2$ and 6 patients without non-squamous histology were excluded from further matching process.

# Estimation of a Control Arm (REVEL) using methodologies

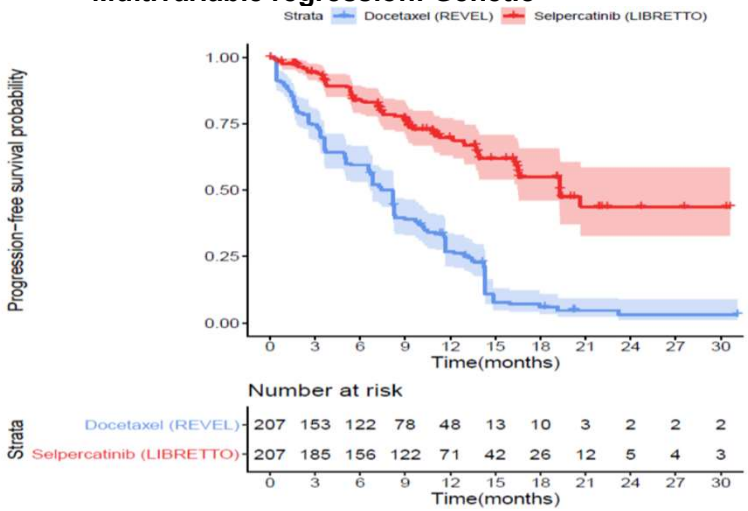
- **Multivariable regression: Propensity score matching**



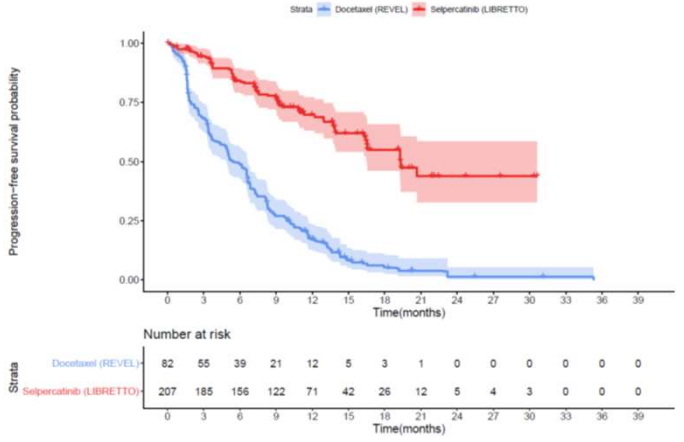

Propensity score weighting using a generalized boosted model (PFS)




- **Multivariable regression: Genetic**

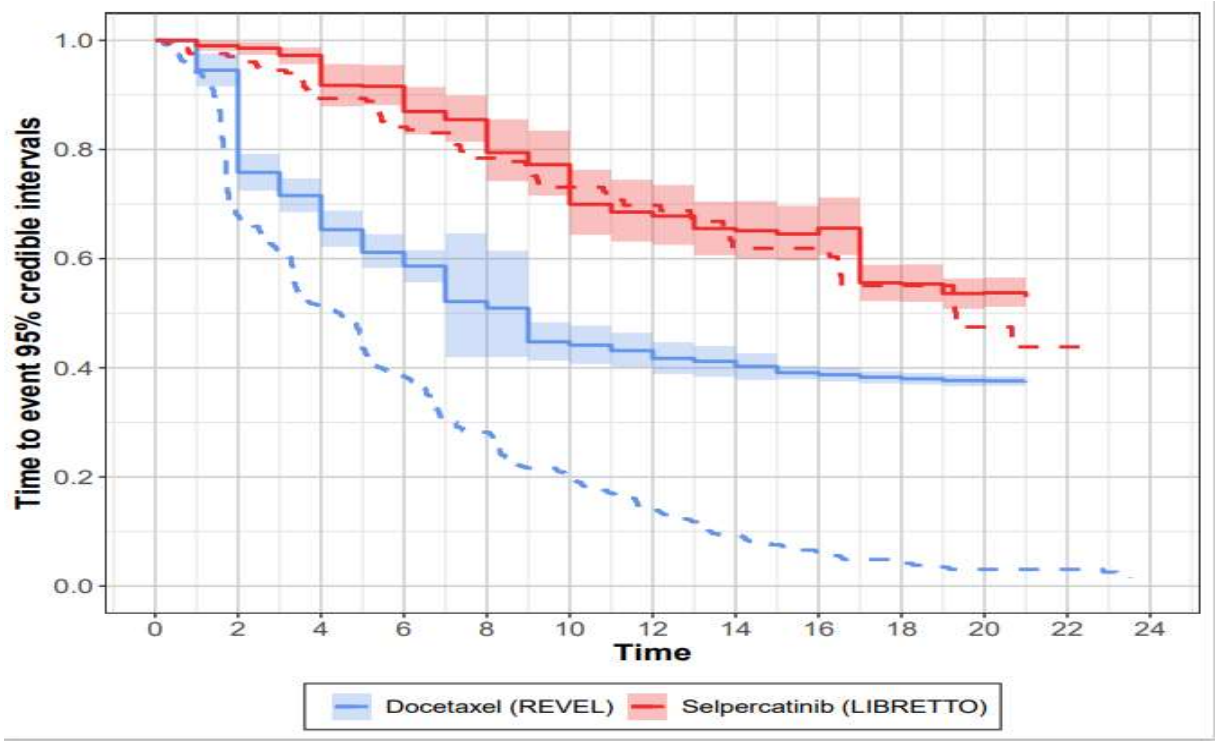



Propensity scores estimated from logistic regression (PFS)




*g the use of statistics*

# Estimation of a Control Arm (REVEL) using TMLE




PFS Cox HR = 0.39, 95% CI: 0.29-0.52, p = <0.0001

# Results - PFS

| Methodologies | HR | 95%CI | P-value |
|---|---|---|---|
| Targeted minimum loss-based estimation (TMLE) | 0.39 | 0.29 - 0.52 | < 0.001 |
| Multivariable regression: Propensity score matching | 0.21 | 0.16 - 0.27 | < 0.001 |
| Multivariable regression: Genetic matching | 0.27 | 0.20 - 0.35 | < 0.001 |
| Propensity score weighting: a generalized boosted model | 0.24 | 0.17 - 0.32 | < 0.001 |
| Propensity score weighting: a logistic regression | 0.24 | 0.17 - 0.32 | < 0.001 |

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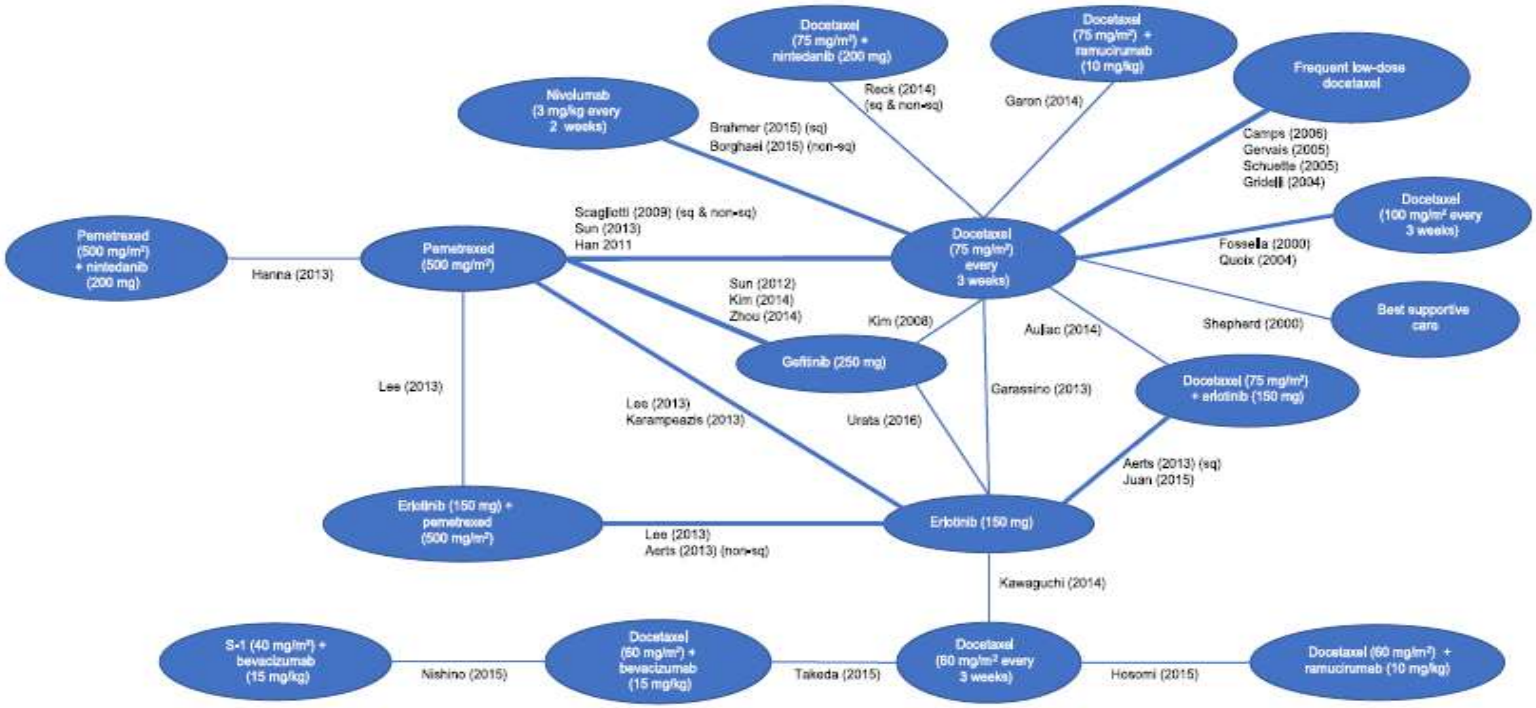
# Clinical Data for Comparators

- Survival Network Meta-analysis (Vickers et al., 2019) has many trials investigated specifically **second-line treatment**
- An update of this network meta-analysis (NMA) had been planned, including more recent relevant trials
  - LIBRETTO-001 also included, after estimation of a control arm



# Clinical Data for Comparators

## The barriers for Cyramza NSCLC indication

- To incorporate differences across populations & trial designs

Ex. The following comparators were specified in the NICE (UK payer agency) scope for Cyramza NSCLC indication:

| Abbreviation | Full name and dose | Patient subpopulation | |
|---|---|---|---|
| RAM + DOC | Ramucirumab 10 mg/kg + Docetaxel 75 mg/m$^2$ | All populations | REVEL Direct evidence |
| NIN + DOC | Nintedanib 200 mg + Docetaxel 75 mg/m$^2$ | Non-squamous | |
| ERL | Erlotinib 150 mg | FGFR-negative* | |
| DOC | Docetaxel 75 mg/m$^2$ | All populations | |
| NIV | Nivolumab 3mg/kg | PD-L1 expression level, Non-squamous/ squamous | |

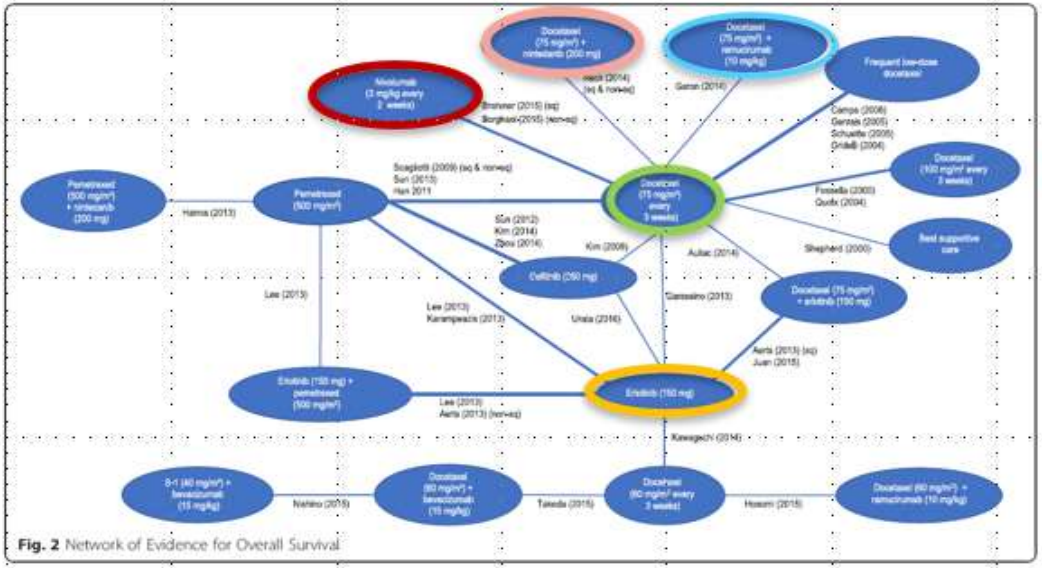


Fig. 2 Network of Evidence for Overall Survival

# Clinical Data for Comparators – pre-treated *RET*+ NSCLC

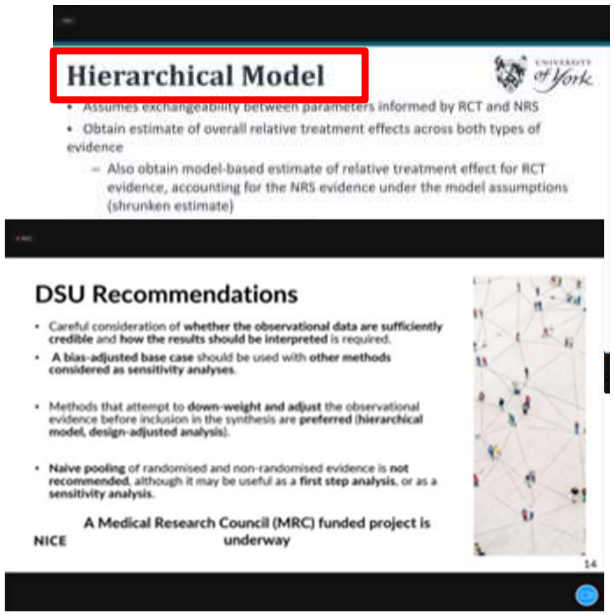
**Solution**

- A NMA of hybrid approach of **fractional polynomials & hierarchical exchange model** was performed to allow different interaction between treatment and population type, where:
  - ERL efficacy was allowed to vary by EGFR status.
  - NIN + DOC efficacy was allowed to vary by squamous histology
  - NIV efficacy was allowed to vary by histology and PD-L1 level

**Methodology evolvement…**

- NICE evaluation research group (ERG) considered that the company provided appropriate justification for using hierarchical models
- NICE accepted the clinical effectiveness of Cyramza submission and **grant <u>end-of-life criteria;</u> willingness to pay threshold increased**.
- The work has been published in BMC Cancer 2019

**A Webinar on 27th of July 2021 by NICE…..**





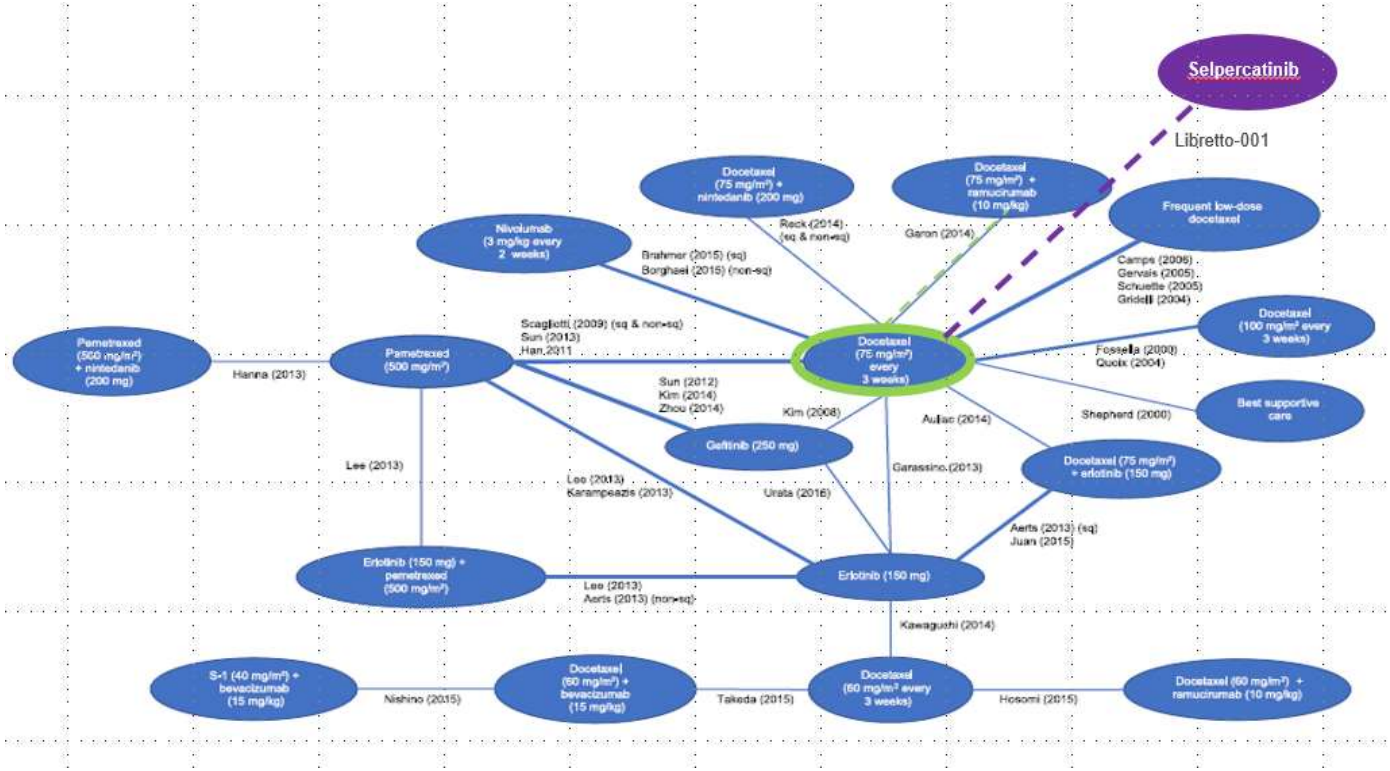
RESEARCH ARTICLE Open Access

Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis

Adrian D. Vickers[1*], Katherine B. Winfree[2], Gebra Cuyun Carter[2], Urpo Kiiskinen[3], Min-Hua Jen[4], Donald Stull[5], James A. Kaye[6] and David P. Carbone[7]

# Clinical Data for Comparators

- Applied NMA of hybrid approach of **fractional polynomials & hierarchical exchange model**



# Prediction vs Actual

Lilly's Retevmo® (selpercatinib) Phase 3 Results in RET Fusion-Positive Non-Small Cell Lung Canc
Thyroid Cancer Both Published in T
Medicine and Presented in a Presic
Congress 2023

October 21, 2023

| PFS | Predicted (2019) | Actual (2023) |
|---|---|---|
| HR | 0.424 (0.289,0.623) | 0.465 (0.309, 0.699) |

*- In the Phase 3 LIBRETTO-431 study, Retevmo more than doubled progression-free survival (PFS) compared to chemotherapy plus pembrolizumab in patients with advanced or metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC)*

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*- In the Phase 3 LIBRETTO-531 study, Retevmo provided a 72% improvement in PFS compared to cabozantinib or vandetanib in patients with advanced or metastatic RET-mutant medullary thyroid cancer (MTC)*

# Limitations

- These are exploratory and hypothesis generating, suggesting what may be observed in a RCT, but should be confirmed in that setting
- Real-world evaluation of response does not adhere to RECIST and may measure different concepts
- Sample sizes for Analytic Strategy 1 were small, there were few events, and analyses were limited
- Weighting factors for these smaller samples could have influenced these results (inflated or decreased p values)
- Estimating a control arm in a different patient population requires several steps and each has a source of error

# Conclusions

- Clinical
  - ✓ Despite the limitations, the consistency of results across multiple analyses of the RW and clinical trial control cohorts
  - ✓ While there may be a unique prognostic effect of RET fusion + status, it is unlikely to be strong enough to explain the large differences in observed outcomes between Libretto-001 and the alternative RW and clinical trial control cohorts

# Conclusions

- Statistical
  - ✓ With careful plannings, the proposed two-fold approaches enabled single-arm trials to estimating comparative efficacy to compare indirectly with other available treatments with good precisions.
  - ✓ Results also may be used to serve as a reference for the efficacy of existing treatments for patients with a particular tumor type, where only mixed population evidence so far exists.
  - ✓ The hybrid approach should help inform the decision-making process for prescribing currently available treatments and could be used to help power future trials.

# Reference


- Rolfo C, Hess LM, Jen MH, Peterson P, Li X, Liu H, Lai Y, Sugihara T, Kiiskinen U, Vickers A, Summers Y. External control cohorts for the single-arm LIBRETTO-001 trial of selpercatinib in RET+ non-small-cell lung cancer. ESMO Open. 2022 Aug;7(4):100551. doi: 10.1016/j.esmoop.2022.100551. Epub 2022 Aug 2. PMID: 35930972; PMCID: PMC9434413.
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