# Quantifying Bias in Matching adjusted indirect comparisons (MAICs): a case study with entrectinib in metastatic ROS-1 positive Non-Small Cell Lung Cancer (NSCLC)

MSR156

Cyril Esnault [1], Louise Baschet [2] Vanessa Barbet [2], Maurice Pérol [4], Katia Thokagevistk [1], David Pau [1], Matthias Monnereau [2], Lise Bosquet [5], Thomas Filleron [6,7]

1. Roche SAS, Boulogne-Billancourt, France; 2. Horiana, Bordeaux, France; 3. Medical oncology department, Centre Léon Bérard, Lyon, France; 5. Health data and partnership department, Unicancer, Paris, France; 6. Biostatistics & Health data science unit, Institut Claudius Régaud IUTC-O. Toulouse, France; 7. Université Paris-Saclay, CESP, INSERM U1018 Oncostat, labeled Ligue Contre le Cancer, Villejuif, France

## Context

The acceptability of indirect treatment comparisons (ITCs) for health technology assessment (HTA) is very challenging because many biases can alter treatment effect estimates, including selection bias, confounding bias, and data quality. There are many recommendations for either correcting or assessing potential biases arising from ITCs. Residual bias due to unmeasured confounders or missing not at random values can be addressed by quantitative bias analysis (QBA). Bias plots, E-values and tipping point analyses are increasingly used to support the primary results of ITCs, but not for Matching Adjusted Indirect Comparisons (MAIC). (1,2)

## Objective

This project aims to explore sensitivity and bias analyses to better support the primary results of MAICs applied to ROS1-positive first-line metastatic NSCLC patients, comparing aggregate data from entrectinib clinical trials (3) and the French national ESME lung cancer cohort.

## Methods

Aggregate data of patients treated with entrectinib in 1L were compared with individual patients data of patients treated with French HTA recognized comparators (chemotherapies +/- bevacizumab) in the ESME database. Weights were estimated using logistic regression and method of moments on age, gender, ECOG Performance Status (PS), smoking status and brain metastases. Multiple imputation were used for ECOG PS (47%) and smoking status (7%) missing values.

As post-hoc sensitivity analyses, residual bias from potential unmeasured confounders was explored using QBA methods with bias plot and E-value. (4,5)

To assess the robustness of the results to the assumption of missing at random data (MAR), tipping point sensitivity analyses were used. These analyses aimed at identifying the distribution of missing ECOG PS in the ESME French HTA population that would be required to nullify or reverse the HR estimated using multiple imputation under MAR assumption. To simulate worse than expected ECOG PS, we included δ-shifts with multiple imputation. (6) The same was applied to smoking status. In addition, we performed analyses with extreme replacement scenarios, and on complete cases.

## Results

In the ESME database, 30 patients were selected when applying inclusion/exclusion criteria aligned with the 60 patients from the 3 entrectinib clinical trials, in first line. After weighting, the effective sample size was 24 for the standard French treatments arm.

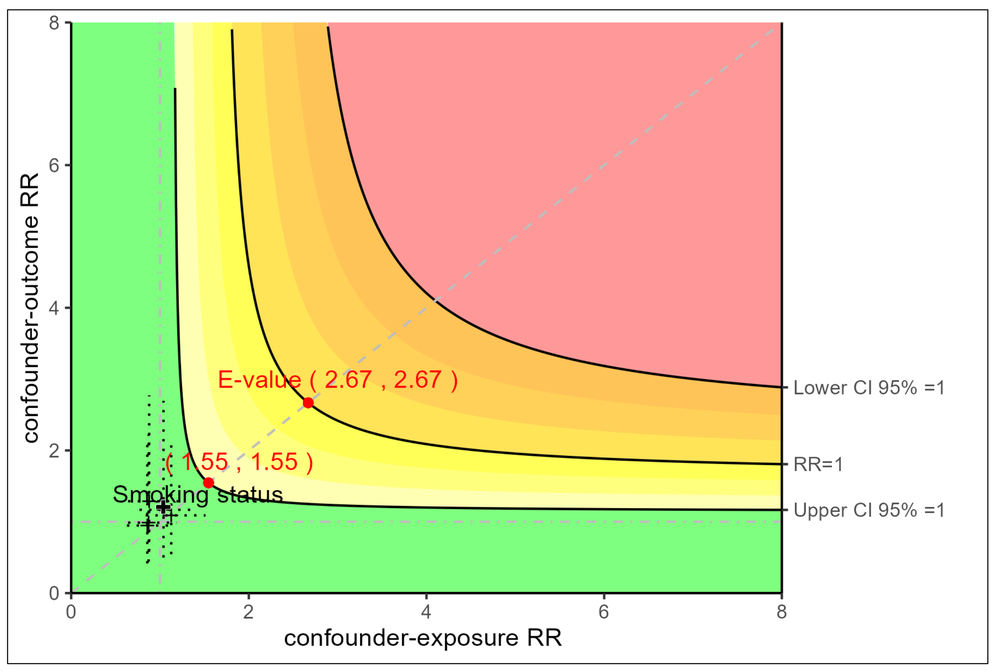
The primary results showed a progression-free survival benefit for entrectinib as first-line therapy compared with standard French treatments (HR: 0.49, p-value<0.01).

### Bias analysis of potential unmeasured confounders

The graph A plots unconfounded treatment effect estimates as risk ratios after adjusting for a hypothetical unmeasured binary confounder over a range of confounder-exposure and confounder-outcome associations on the risk ratio scale.

An E-value of 2.67 was estimated, which is higher than the strongest observed association with outcome and treatment (risk ratios for smoking status of 1.29 and 1.44, respectively).

*A. Bias plots from a weighted Cox model showing unmeasured confounding for comparison between the 1L entrectinib arm and 1L French HTA recognized comparators.*




*The colors map the strength of an unmeasured confounder (x and y axes) to the robustness of this study's conclusions (color gradient). The yellow area corresponds to a non statistically significant effect in favor of entrectinib.*
*The E-value corresponding to HR of 0.49 (approximate risk ratio, 0.61) was 2.67, representing confounder-PFS and confounder-exposure correlations needing to be simultaneously greater than 2.67 on the risk ratio scale to move the HR point estimate to 1 and reverse our conclusion.*

### Bias analysis of potential impact of Missing Not at Random data

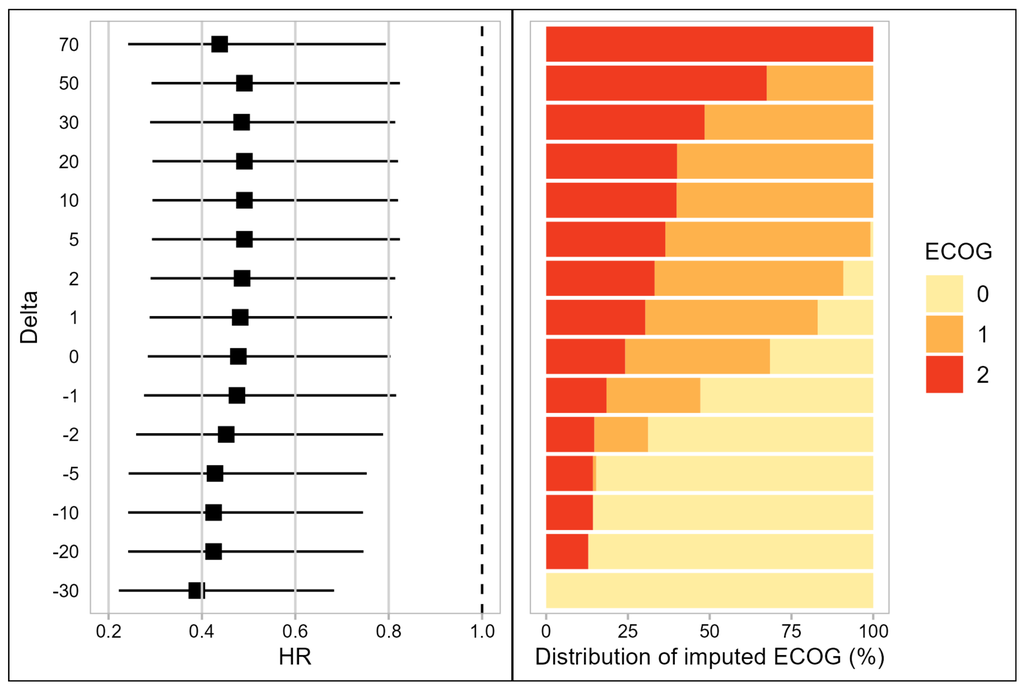
Several delta values have been tested to obtain the range of all possible distributions of ECOG PS, see figure B below (on the left, the weighted Cox HR on PFS in 1L HTA population with 95% CI and p-values, according to delta values; on the right side, the corresponding distribution of imputed ECOG PS scores). **No tipping point was reached**.

In addition, extreme scenarios were considered. For ECOG PS, by replacing the 14 missing values (out of 30) by a fixed value (0, 1 or 2), the conclusions are unchanged (HR: 0.39 [0.22, 0.68], resp. 0.50 [0.29, 0.86], resp. 0.44 [0.24, 0.79]).

The same analyses were performed for the 2 missing values of the smoking status with similar results on the robustness of the primary result to missing values.

Finally, the primary result was robust to complete case analysis (HR: 0,40 [0.21, 0.73]).

*B. Tipping point-based bias analysis assuming non-random missingness for ECOG PS for comparison between the 1L entrectinib arm and 1L French HTA recognized comparators (50 imputed datasets)*




## Conclusion

**This study presents the first comprehensive applications of quantitative bias analysis to MAICs. It demonstrates the usefulness of these approaches in supporting the robustness of the efficacy results of MAICs to residual bias and missingness assumptions, even in the presence of a limited sample size.**

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