

Addressing Treatment Switching Bias with G-methods: Exploring the Impact of Model Specification

Amani Al Tawil^{*1,2}, Sean McGrath³, Robin Ristl^{†4}, and Ulrich Mansmann^{†1,2}

¹*Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, Ludwig-Maximilians-Universität München*

²*Pettenkofer School of Public Health, Faculty of Medicine, Ludwig-Maximilians-Universität München*

³*Department of Biostatistics, Harvard T.H. Chan School of Public Health*

⁴*Center for Medical Data Science, Medical University of Vienna*

Electronic Supplementary Material 6

Survival and Forest Plots

*Correspondence: altawil@ibe.med.uni-muenchen.de

†Equally contributed

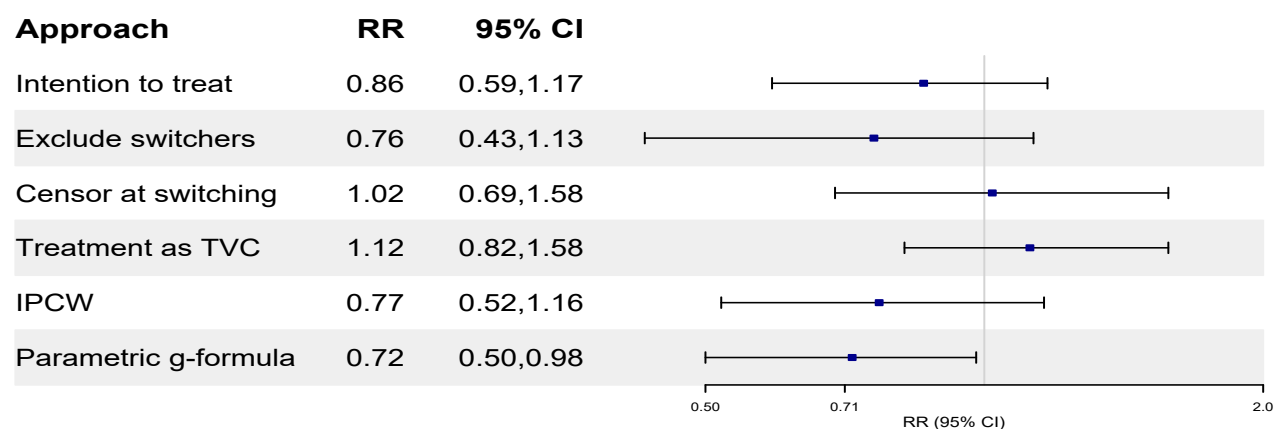
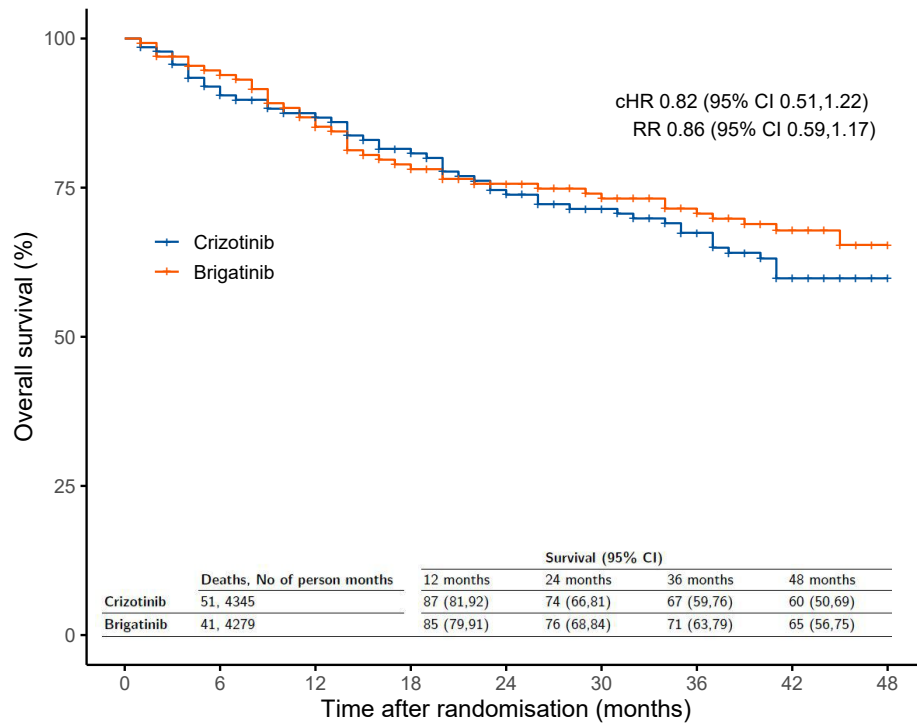
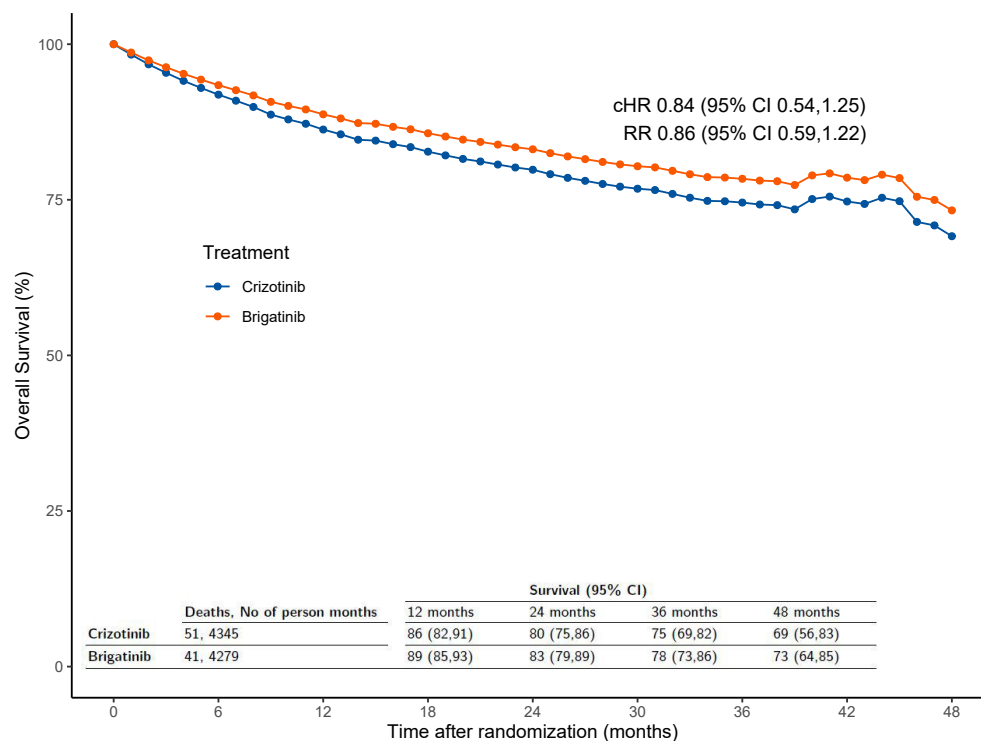


Figure S1: Forest plot of RR and their 95% CI for the effect of brigatinib versus crizotinib on OS investigated through various modelling approaches. RRs for the ITT, exclude switchers censor at switching and including treatment as a TVC analyses were estimated from a pooled logistic regression model. RR for the IPCW approach was estimated using a weighted pooled logistic regression model using the product of the two weights for switching (specifications 4 in Table 4) and LTFU/AC (specifications 4 in Table 6). RR from the parametric g-formula were estimated from specification 1 in Table 7. 95% CIs were estimated using a non-parametric bootstrap procedure based on 1000 samples for all approaches and 500 samples for the parametric g-formula



(a) Kaplan-Meier survival curves comparing overall survival between “assign to brigatinib” and “assign to crizotinib” and assuming non-informative censoring; Survival probabilities are derived from the KM estimator, Cumulative Hazard Ratios (cHRs) and Risk Ratios (RRs) are estimated from a pooled logistic regression model



(b) Parametric survival curves standardized for baseline covariate distribution from a pooled logistic regression comparing overall survival between “assign to brigatinib” and “assign to crizotinib” and assuming non-informative censoring; Cumulative Hazard Ratios (cHRs), Risk Ratios (RRs) and survival probabilities are estimated from a pooled logistic regression model standardized for baseline covariate distribution

Figure S2: Overall survival: ITT

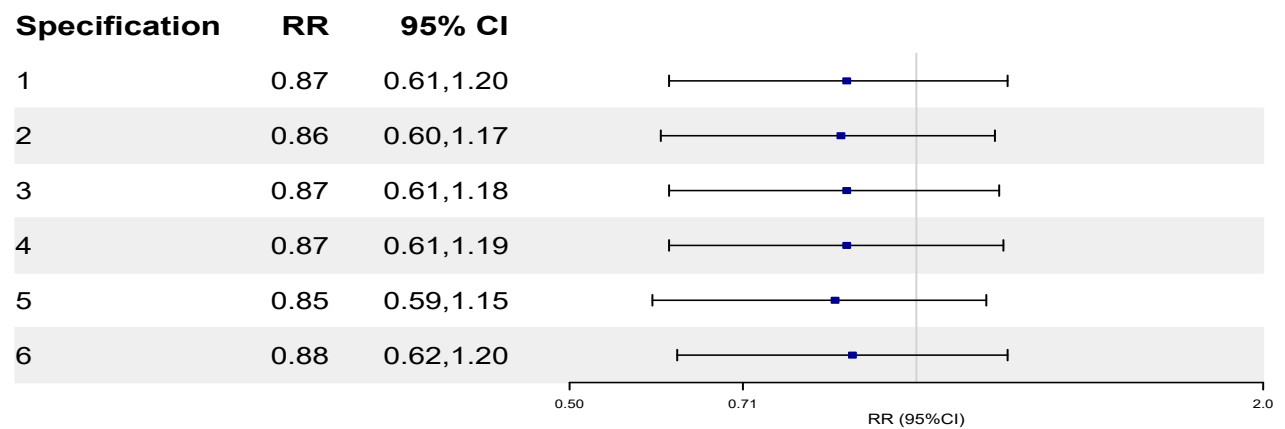
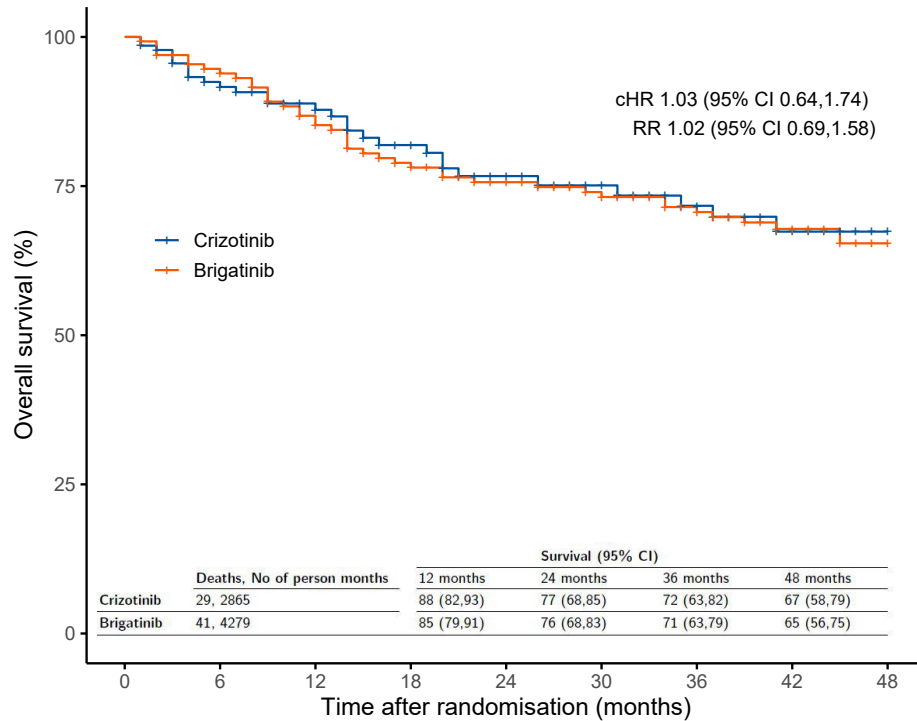
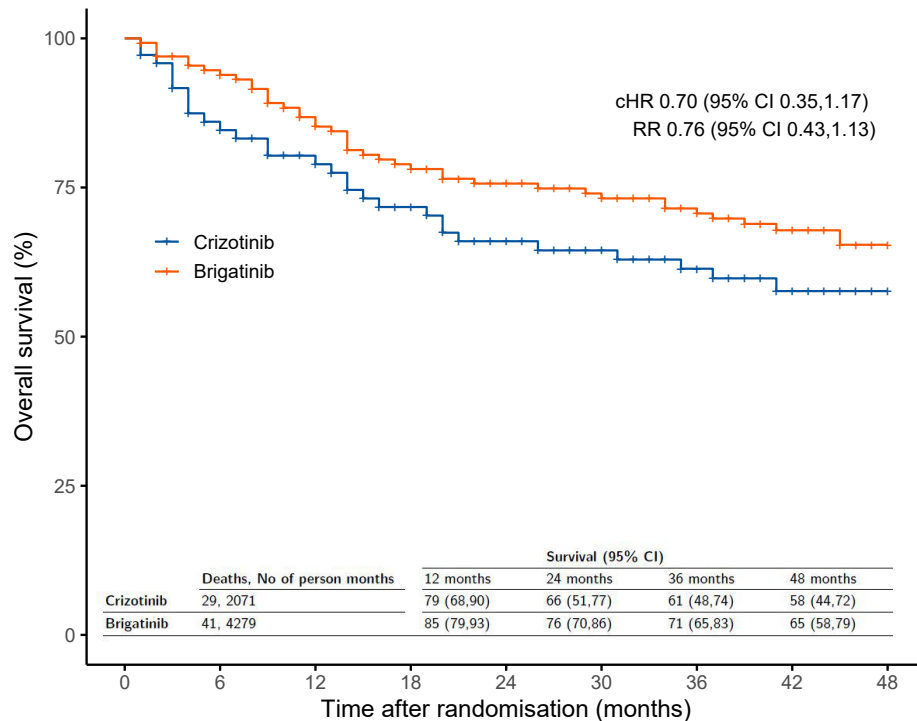


Figure S3: Forest plot of RR and 95% CI for the Causal effect of “assign to brigatinib” versus “assign to crizotinib” on OS investigated through specifications 1 to 6 using IPCW. Death is censored by LTFU/AC. RRs were estimated from a weighted pooled logistic regression using weights for LTFU/AC and formulated as the ratio of the cumulative risks by month 48. Reported CIs were estimated using a non-parametric bootstrap procedure based on 1000 samples. cHR, cumulative hazard ratio; CI, confidence interval; OS, overall survival, IPCW, inverse probability of censoring weights; LTFU, loss to follow up; AC, administrative censoring



(a) Overall survival: Censoring at switching



(b) Overall survival: Excluding switchers

Figure S4: Kaplan-Meier survival curves comparing overall survival between “always Treat with Crizotinib” and “always Treat with brigatinib” and assuming non-informative censoring; Survival probabilities are derived from the KM estimator, Cumulative Hazard Ratios (cHRs) and Risk Ratios(RRs) are estimated from a pooled logistic regression model; In panel (a) switchers were excluded; In panel (b) switchers were censored at switching

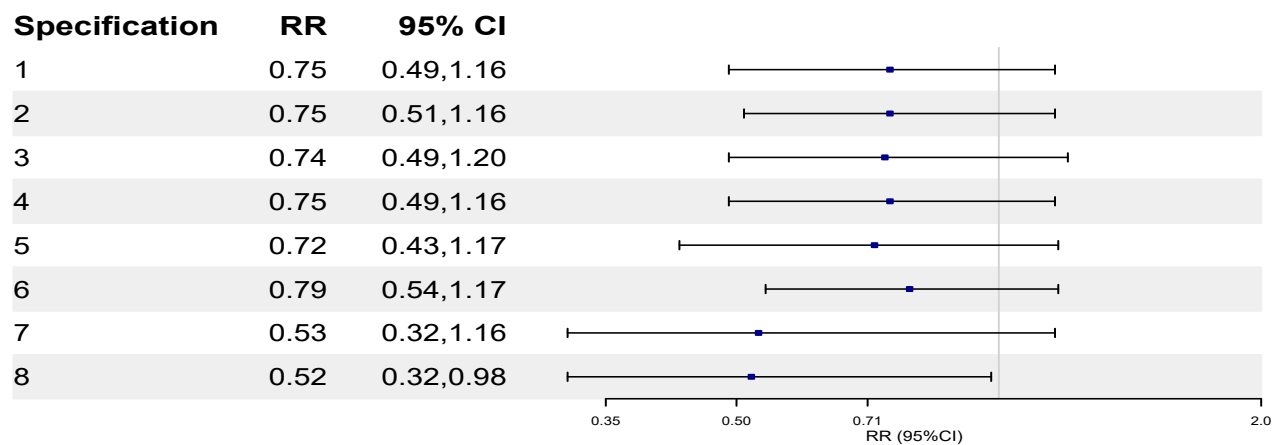


Figure S5: Forest plot of RR and 95% CI for the causal effect of “always treat with brigatinib” versus “always treat with crizotinib” on OS investigated through specifications 1 to 8 using IPCW. LTFU is assumed at random; Death is censored by a minimum of treatment switching and LTFU/AC and formulated as the ratio of the cumulative risks by month 48. Reported CIs were estimated using a non-parametric bootstrap procedure based on 1000 samples. cHR, cumulative hazard ratio; CI, confidence interval; OS, overall survival, IPCW, inverse probability of censoring weights

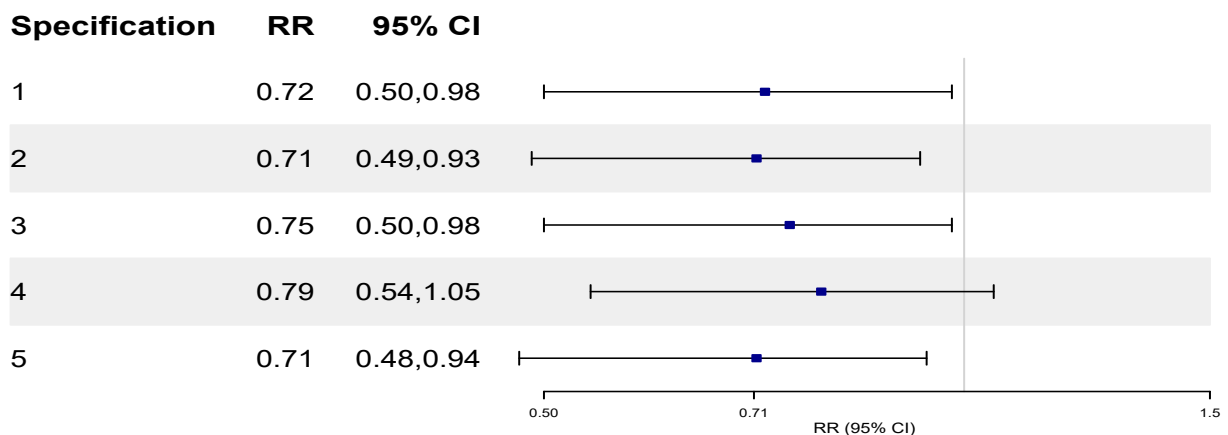


Figure S6: Forest plot of RR and their 95% CI for the causal effect of “always treat with brigatinib” versus “always treat with crizotinib” on OS investigated through specifications 1 to 5 using the parametric g-formula. Reported CIs were calculated using a non-parametric bootstrap procedure based on 500 samples (with 60 replicate failures observed for specification 4)