Treatment crossover refers to the situation in randomised controlled trials (RCTs) where patients randomised to the control group switch to the experimental treatment. This leads to biased estimates of treatment effects if crossover is not appropriately controlled for. Several crossover adjustment methods are available, but previous research has shown that the optimal adjustment method depends upon the characteristics of the trial [1]. This study applies crossover adjustment methods to an RCT comparing trametinib to chemotherapy in patients with BRAF V600E/K mutation-positive advanced or metastatic melanoma (NCT01245062), and investigates which adjustment method best fits this case study. Patients enrolled in the METRIC clinical trial were randomised 2:1 to receive trametinib 2 mg once daily or chemotherapy (DTIC or paclitaxel). There were 273 patients in the primary efficacy population (trametinib, n = 178, chemotherapy, n = 95) and 64 (67.4%) chemotherapy control group patients switched onto the experimental treatment.

**Objectives**

- To evaluate the crossover adjustment methods to determine which is most appropriate for this trial.
- To assess the impact of crossover on treatment effect estimates.
- To compare the performance of different crossover adjustment methods.

**Methods**

**RPSFTM & IPE Algorithm**

The standard single parameter RPSFTM (Rank Preserving Structural Failure Time Model) and the IPE (Iterative Parameter Estimation Algorithm) split the observed event time, \( T_{on} \), into time spent "on" treatment (\( T_{on} \)) and time spent "off" treatment (\( T_{off} \)). Counterfactual event times, \( U_i \), are calculated, and are related to observed event times with the following causal model:

\[
U_i = T_{off_i} + e^{\phi_0} T_{on_i}
\]

Where \( e^{-\phi_0} \) represents the acceleration factor associated with the intervention – the amount by which expected survival time is increased by treatment.

**IPCW**

The IPCW (Inverse Probability of Censoring Weights) involves censoring switchers at the time of treatment switch, and weighting remaining patients according to their similarity to switchers, using information on baseline and time-dependent covariates. A weighted Cox regression model is utilised to estimate an adjusted hazard ratio. A weighted Kaplan-Meier curve can also be obtained.

**IPW**

The IPW (Inversely Weighted) approach weights switchers at the time of treatment switch, and weighting remaining patients according to their similarity to switchers, using information on baseline and time-dependent covariates. A weighted Cox regression model is utilised to estimate an adjusted hazard ratio. A weighted Kaplan-Meier curve can also be obtained.

**Key model requirements:**

- No unmeasured confounders: need data collected at baseline and over time on all variables that are prognostic of switching or survival.
- E.g. patient choice as to whether to switch.
- Correctly specified models for switching and survival.

**Results**

- In the primary efficacy population, the unadjusted hazard ratio (HR) for overall survival (OS) was 0.72 (95% Confidence Interval 0.52 – 1.01) in the GSK analysis.
- Point-estimates of the adjusted HRs produced by the most plausible crossover adjustment methods ranged between 0.48 and 0.53, consistently favouring trametinib.
- In the first-line metastatic subgroup, the most suitable adjustment methods resulted in HR point estimates ranging from 0.44 to 0.55, compared with the unadjusted HR of 0.74 (95% CI 0.49 – 1.12) in the GSK analysis.
- The results were sensitive to the technique used to apply each method. Key issues included recensoring, the active nature of the comparator and the choice of covariates included in the analyses.

**Conclusions**

- Each of the crossover adjustment methods result in a lower HR than the unadjusted analysis, showing improved OS benefit of trametinib compared to chemotherapy.
- However, the crossover-adjusted results are dependent on key assumptions. It is important to analyse trial characteristics and model output carefully when identifying which applications of the adjustment methods are most plausible.
- RPSFTM and IPE methods require a non-active comparator, which is not ethically feasible in this case. They also rely on the common treatment effect assumption, which may be implausible if the capacity to benefit from treatment is reduced after disease progression.
- The estimates produced using the RPSFTM and two-stage method to reduce bias by breaking the dependence between censoring time and treatment; but in the METRIC trial, recensoring is considered inappropriate because it will exacerbate the bias arising from the changing treatment effect over time.

**References**


This work was based on a report which was funded by GlaxoSmithKline.