**ABSTRACT**

Most Phase III oncology clinical trials include Overall Survival (OS) as a key endpoint. The analysis of OS following intention-to-treat (ITT) principle is considered the ‘gold standard’, but many times this approach is not the most appropriate. A typical example occurs when control arm patients can be switched to the experimental arm once they have documented disease progression. In that case, ITT comparison underestimates the actual OS difference between treatment groups. Several alternatives, from naïve to more complex methods, have been proposed to measure the crossover impact.

This poster presents a SAS program to perform one of the best possible approaches to mitigate the crossover impact, “the two-stage method” proposed by Latimer et al.

**BACKGROUND MATERIAL**

The two-stage method provides a good fit to treatment change mechanics often observed in oncology. Usually, switching is only permitted after progressive disease (PD). If it occurs shortly afterwards, PD can be used as a secondary baseline for patients in the control group. Fitting a parametric model would be expected to produce a reasonable estimate of the effect resulting from crossover, provided that the model fits the data and some pivotal assumptions are met. The resulting acceleration (deceleration) factor associated with treatment change represents the additional post-progression survival achieved because of treatment change and could then be used to “shrink” survival times in switching patients to derive a counterfactual survival dataset upon which standard survival analysis could be undertaken.

The main assumptions for the two-stage method are:

- Crossover occurs soon after PD.
- The characteristics of patients that switch and do not switch are comparable at the time of PD.
- No unmeasured confounders at the time of crossover are present.

The dataset ‘myeloma’ from SAS help library is used with some artificial changes, see the associated paper. (https://support.sas.com/documentation/cdl/en/statug/65392/HTML/default/viewer.htm#statug_phreg_sect046.htm)

The two-stage method can be applied. As any method it may have implicit limitations caused by the assumptions that have to be met and the creation of a counterfactual distribution. Several penalizations to the acceleration factor should be applied to check the robustness of the results.

**CHECK OF MAIN ASSUMPTIONS**

- Crossover occurs soon after PD. The time between PD and crossover can be calculated and summarized descriptively.
  
<table>
<thead>
<tr>
<th>Time to crossover from PD (months)</th>
<th>N</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
<td>0.55</td>
<td>0.25</td>
<td>2.90</td>
</tr>
</tbody>
</table>

- The characteristics of patients that switch and do not switch are comparable at the time of PD.

PROCEDURE

The SAS LIFEREG procedure will be used to adjust a parametric distribution for the post progression survival data of the control arm patients. The most widely used distribution is the Weibull distribution but other different distributions can be tested and then compared them by means of -2Log Likelihood or AIC/BIC selecting the distribution with better adjustment.

As any method it may have implicit limitations caused by the assumptions that have to be met and the creation of a counterfactual distribution. Several penalizations to the acceleration factor should be applied to check the robustness of the results.

CONCLUSIONS

The two-stage method is a valid approach to obtain adjusted estimates of the OS effect in oncology clinical trials with treatment switch, provided that there is a good fit of the parametric models and the method assumptions are plausibly met.

For an actual application example in a Phase III trial. See the ADMYRE trial adjustment results presented as an Oral Poster Session at the congress of the American Society of Clinical Oncology - ASCO 2018 (Abstract #8018).

Your comments and questions are valued and encouraged.

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