FROM THE JOURNALS

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COMPARATIVE-EFFECTIVENESS RESEARCH/HTA

Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study

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In determining the cost-effectiveness of a novel oncology drug relative to the current standard of care (SoC), decision models have to estimate the patients' outcomes (eg, response, progression-free survival overall survival), the resulting quality of life, and the associated costs over the expected patient lifetime. However, efficacy estimates are based on data from randomized controlled trials (RCTs), which cover a much narrower time span (typically 3 to 5 years) and are often immature due to the limited number of events observed, thus requiring extrapolation.

Extrapolation is especially critical for overall survival, a key driver of cost-effectiveness. It is further complicated by the recent advancements in cancer treatment, namely immune-checkpoint inhibitors (ICIs), which may result in a proportion of patients achieving long-term survival (sometimes referred to as the "statistically cured" fraction). The accuracy of the extrapolation can be a deal-breaker for the cost-effectiveness of a therapy.

This article investigates the issue using the guidance published by the United Kingdom's National Institute for Health and Care Excellence (NICE) on the first licensed ICI ipilimumab for patients with treatment-naive advanced melanoma. Authors revisit the original assessment based on 3-years' worth of survival data using updated data (5-years' survival data) from the pivotal trial to assess the accuracy of the extrapolation methods used and to compare these to alternative extrapolation techniques with the objective of establishing whether an alternative extrapolation may have provided more accurate survival projections.

The original method used for survival extrapolation included a piecewise survival model of 3 components: (i) KM curve from a pivotal trial up to 24 months, (ii) a log-normal curve fitted to OS data over 2 to 5 years, and (iii) a Weibull curve fitted to long-term registry data. In addition, the authors also considered alternative extrapolation methods that are commonly used for oncology cost-effectiveness modelling: a standard parametric survival; a Royston and Parmar spline-based model; and mixture cure/noncure models.

All these methods are applied on 3-years' survival data, and for each method the underlying hazard function is evaluated to establish the method's applicability with respect to the observed data. The 5-years' predictions derived from each of these methods were then compared to a longer trial data-cut (5 years) while 10 to 15 years' survival prediction are compared to external real-world evidence (AJCC data) to assess clinical plausibility and validity.

Based on the initial investigation of the hazard functions estimates in the 3-year data cut, only parametric models that can accommodate increasing and then decreasing hazard were deemed appropriate. Focusing on 5-years' survival prediction, only the piecewise model and the mixture cure models (MCMs) provided estimates relatively close to the observed ones (14.4%-17.5% versus 18.1% observed).

However, the original survival piecewise predictions and MCMs diverged significantly post 5 years and remain challenging to assess which of the 2 models performs best, given that the comparability of patient characteristics between the pivotal trial and American Joint Committee on Cancer (AJCC) data is unknown. The authors concluded that only models incorporating an element of external information (through a cure fraction combined with background mortality rates or using registry data) provided accurate estimates of 5-year survival. On the contrary, flexible models that were able to capture the complex hazard functions observed during the trial, but which did not incorporate external information, extrapolated poorly.

This study is of interest to both researchers and decision makers concerned with the challenges of selecting the most appropriate survival function for therapies that have new mechanisms of action. With many options beyond the simple parametric extrapolations that were once the standard, one needs to look beyond the trial data and rely on external evidence. Although the generalizability from a single case study is difficult, this study clearly examines and details the process of survival distribution fitting and validity assessment itself. While the conclusion regarding the specific model performing best would definitely vary across individual as well as oncology indications, the steps to follow for selecting the most appropriate extrapolation will remain the same. This paper is a valuable companion in walking through the complex task of selection and shows the importance of extensive validation of survival outcome extrapolation that eventually will lead to an optimal decision regarding the adoption of new therapies.