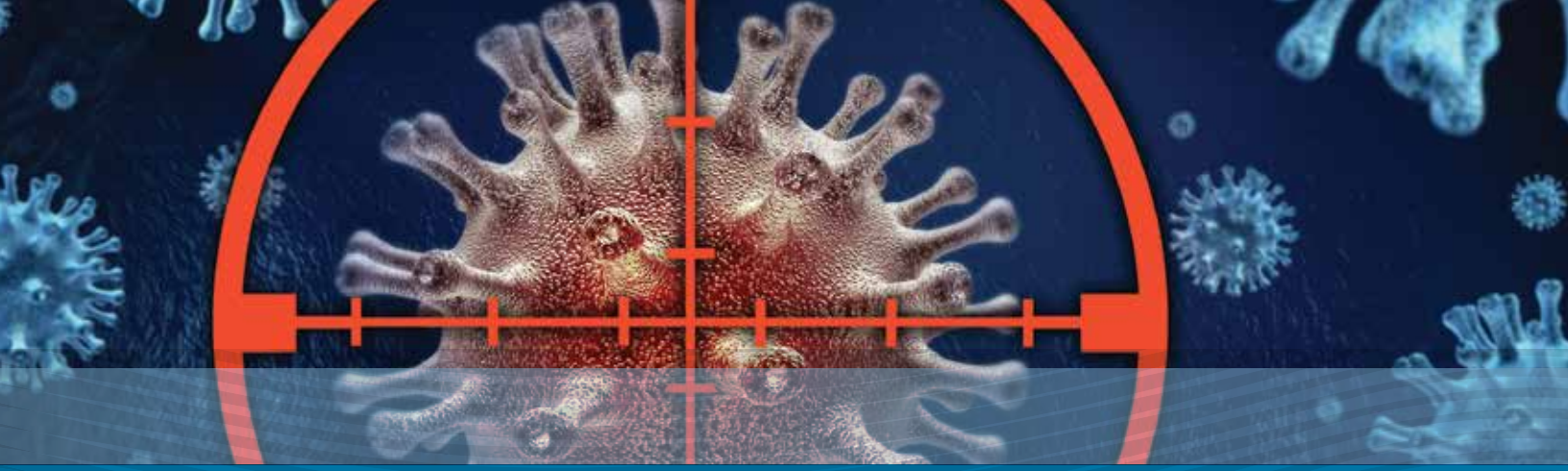

Projecting Overall Survival with Immuno-Oncology Treatments

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Introduction

On February 4, 2016, the American Society of Clinical Oncology (ASCO) announced immunotherapy as the top cancer advance of the year.[1] As an alternative to traditional chemotherapies and targeted therapies, scientists and doctors are increasingly suggesting immunotherapies, including checkpoint inhibitors, transforming the clinical landscape and patients' lives. Differing substantially from traditional chemotherapies, immunotherapies induce the patient's immune system to produce an anti-tumor response. Checkpoint inhibitors block certain T-cell receptors, such as CTLA-4 (e.g., ipilimumab), PD-1 (e.g., pembrolizumab, nivolumab) and PD-L1 (e.g., atezolizumab, avelumab, and durvalumab), which act as "checkpoints" regulating T-cell activation. Inhibiting the action of these receptors promotes T-cell activation and anti-tumor response, possibly even tumor rejection.[2]

As experience with immunotherapies in other oncology areas is growing, questions have emerged regarding challenges in the assessment of the value of these therapies. The most visible challenge is in extrapolating overall survival (OS). In some indications, the new checkpoint inhibitors, either as monotherapy or as combination therapy, provide substantial survival benefits, and the OS curve appears to plateau for an important proportion of patients (20-25% in previous trials for PD1 and PDL 1 inhibitors).[3,4] This suggests that many patients could potentially be cured of their disease (but of course, still subject to other mortality). This presents several difficulties, as the shape of the OS Kaplan-Meier curve often does not conform to the conventionally used distributions[5,6] and the proportional hazard assumptions required for conventional network meta-analyses (NMAs) do not hold. In addition, the follow-up in the trials is relatively short and there is no long-term experience with these therapies (the first checkpoint inhibitor, ipilimumab was approved in 2011 by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in advanced melanoma. Thus extrapolation of OS presents new challenges.

This article reviews different methods for the projection of OS, covering both standard approaches and extensions to deal with the expected challenges to model survival with immunotherapies.

Standard Statistical Methods

Parametric survival analysis methods are the standard approach for modeling and projecting time-to-event outcomes. This involves testing various statistical distributions, such as the exponential, Weibull, Gompertz, Gamma, Log-Logistic, and Log-Normal distributions, and assessing their suitability for projection based on fit statistics and contextual/clinical considerations. For instance, a suitable fit may be chosen based on whether the predicted curve obtained from the parametric models align with the observed curve over the observation window and if the long-term shape and properties (e.g., longest survival, expected event time) align with clinical opinion.

Parametric modeling can work in a broad range of scenarios, but may not produce an adequate projection in cases where the underlying risk functions are complex. The case of survival with immuno-oncology treatments may be such a case due to the shape of mortality curves. For instance, in a trial of ipilimumab in patients with advanced melanoma,[7] the OS curve dropped rapidly in the first 12 months, reaching the median at 11.4 months and plateauing at 3 years with 22% still alive. Follow-up continued to year 7 with the curve only dropping down to 17%. A similar pattern can be seen in the OS observed in the nivolumab arm of the CHECKMATE-017 trial[8] in advanced squamous non-small-cell lung cancer (NSCLC); the OS curve dropped quickly in the first 9 to 12 months and then started to plateau. Capturing both high early mortality and gradual deceleration to a steady rate can be difficult to fit with a single parametric function.

Piecewise parametric fitting is a more flexible alternative and may improve fit. This consists of fitting the OS curves in segments by dividing the time axis to allow the distribution being fitted to have different parameter values in each part. In the NICE appraisal of nivolumab for previously treated locally advanced or metastatic squamous NSCLC[9], 2-knot spline analysis was conducted to fit distributions to the OS curve since none of the standard distributions provided a good fit. While this can help in fitting the observed pattern more closely, the shape of the long term projection may remain implausible. That is, projecting a flat mortality pattern over a long term may yield life-expectancy estimates that are implausible. Thus, economic models using such projections may have to limit the period over which the fitted curve is applied and revert to alternate means of predicting beyond this window, which may be difficult without additional data or assumptions.

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Other strategies may help overcome these challenges. We discuss some of these in the following sections.

Alternative Strategies

Modeling OS as Sum of TTP and PPS

While the OS curve may be difficult to fit due to long-term survivors, it is possible that patients who have progressed are at greater risk of death. Thus, the post-progression survival (PPS) may be easier to fit with standard distributions. The projection model can incorporate progression time and other patient characteristics so that predicted PPS times are consistent with patients' characteristics.

To derive projected OS with this approach, a projection is also needed for time-to-progression (TTP) so that survival can be predicted for patients not observed to have progressed during the trial. This would also be done using standard parametric modeling. The TTP and PPS projections can be used together to generate individual TTP and PPS predictions, and deriving OS from these.

It is possible, however, that TTP itself may be difficult to project as some patients receiving immuno-oncology treatments may achieve long-term remission, manifesting as a plateau in the curve. Predicting survival for these patients in economic models would require different considerations; for instance, one possibility is to use life tables to model their survival, which would assume these patients are effectively cured. Alternately, some adjustment could be applied to life tables to reflect the impact of disease on survival using additional data from historical controls, for instance.

Landmark Analysis

In landmark analyses, patients are grouped based on patients' status on a marker of their condition at some fixed time point. For instance, the grouping event may be response to treatment. Outcomes like survival can then be assessed in these landmark groupings, after omitting patients who have the outcome prior to the landmark point. This avoids grouping patients at baseline based on a future status, which introduces bias.

Landmark analyses typically aim to estimate treatment effects and assess the impact of the grouping variable on

the effects. This approach can be leveraged for projection of OS by stratifying the population by response status at an appropriate time point following start of treatment (e.g., three months) and fitting parametric models within each of these groups. This modeling would be done directly on OS and would represent projection of conditional survival among those who are alive at the landmark point. The full OS curve can then be reconstructed by combining the projection with the mortality rate prior to the landmark.

While this approach can improve fit for some of the landmark groups, survival in other groups may remain difficult to fit. In particular, some responders may have sustained remission leading to some of the same challenges noted above.

Dynamic Modeling of Response, Progression and Survival

In this approach, a reference group would be identified in which OS can be projected adequately with parametric distributions. For instance, patients who have failed to achieve response may be such a group. A parametric model produces a projected OS for this reference group, but cannot be applied for projections more broadly. To allow for this, the projected curve must be adjusted to the complement of the population (e.g., responders). This requires quantifying the relative OS between the reference group and its complement. A Cox regression model can be used for this, as it allows including both baseline and time-dependent factors (like response), and can incorporate the effect of other relevant events that may impact survival (like progression).

As with the TTP/PPS method, the dynamic modeling approach also requires predicting the intermediate events like response and progression. OS would be reconstructed by combining the reference curves, Cox regression, and projections of the intermediate events.

Parametric Mixture Cure Models

Parametric mixture cure models[10] assume that a fraction of the population may be cured, or at least achieve long-term sustained response, and as a result, have a different mortality risk distribution from others. Outcomes in the cured and non-cured patients are allowed to arise from different underlying models. Thus, the statistical procedure aims to determine which patients will achieve cure, and allows a different parametric function in the two population strata. Thus, projections for patients that are not cured is more likely to produce plausible projections, while projections for patients who are cured may require external data, for instance, general mortality rates, possibly adjusted to reflect that patients have cancer. The key assumption in this approach is the plausibility of a cure in the context being modeled; this can be verified in the data based on the observed pattern of the outcome (long-term flattening of the curve) and a high rate of censoring.

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Discussion

Immuno-oncology treatments can offer significant long-term response and survival. Modeling these outcomes for economic evaluations introduces challenges with the projection of outcomes for economic modeling. Different strategies are possible to help improve fit to ensure cost-effectiveness assessments are accurate. The common feature in the approaches described above is the attempt to enhance fit by separating the population or the time-axis into subsets that may be easier to model. With piecewise fitting, the subsetting is done directly on the time axis without explicitly characterizing which patients are followed through each period. With the TTP/PPS approach, the progression event is used to separate OS into two parts, with the hope of making each of these easier to fit with standard approaches. The landmark analyses group patients based on response, while the dynamic modeling strategy attempts a finer breakdown by incorporating both response and progression, and attempts to model the effects of these events. The parametric mixture cure model subsets the population based on whether they are cured, which in this setting would be interpreted as long-term remission; in addition to projecting survival, the approach can also help understand the profile of long-term survivors. In all cases, challenges can remain in projecting survival in one or more of the subsets created in the analyses – those achieving long-term remission. Additional data, clinical insight, and assumptions may be required to be able to project for the entire population. It is advisable to attempt various approaches and assess the sensitivity of conclusions from economic analyses.

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