Extrapolation of survival curves using external information: implementation of Guyot's method in previously untreated advanced or metastatic renal cell carcinoma

Caswton H1, Genestier V1, Dale P2, Don J3, Malcolm B2

1Amaris, Paris, France; 2Bristol-Myers Squibb, Uxbridge, United-Kingdom; 3Bristol-Myers Squibb, Princeton, NJ, USA

Background

The extrapolation of survival outcomes is key to cost-effectiveness (CE) analyses in oncology, especially when comparing (PFS) and overall survival (OS) outcomes. A number of factors have limited the successful adoption of PFS.

Different parametric models can achieve a comparable fit to the randomised clinical trial (RCT) data but generate different long-term predictions, due to the variability of the tails of survival distributions.

Guidance from the NICE DGU to Latimer (1) suggests that the choice of distribution should be based on internal and external validation, the latter usually being undertaken by visual inspection to inform model choice.

The CheckMate 214 trial is a phase 3, randomised, open-label study of nivolumab combined with ipilimumab in patients with metastatic RCC previously untreated with analgoic immunotherapies. The primary endpoint of the trial was OS and the key secondary endpoints were PFS and OS after 2 years.

Objective

The aim of this study was to evaluate the impact of the use of the method developed by Guyot et al. to include external data in statistical extrapolation models, using survival outcomes from CheckMate 214 in first line advanced or metastatic RCC patients with intermediate to poor prognosis.

Methods

Since mean survival times are very sensitive to assumptions around what occurs after the trial follow-up (in the tail of the survival), there is a need to improve the extrapolation of survival data for use in CE analyses. This paper presents a method developed by Guyot et al. using survival information to extrapolate survival curves on the basis of the CheckMate 214 data, using the following steps:

1. Identification of external data: a systematic literature review on observational studies was conducted to identify relevant data available on CheckMate 214 patients. It is implied to ensure that patient characteristics are as close as possible to trial population, thereby ensuring that prognostic variables are not biased.

2. Definition of constraints: two main assumptions were made on the survival of the comparator arm of CheckMate 214: sunitinib.

3. Conditional survival constraint: the underlying assumption is that the conditional survival in the clinical trial control arm is likely to converge to that of the one observed in observational studies over the long term. This constraint was applied to OS and PFS. The constraint was applied as follows:

\[ \frac{S_{control}(t)_{est}}{S_{control}(t)_{unknown}} = \frac{S_{unknown}(t)_{est}}{S_{unknown}(t)_{estimated}} \]

With a binomial method, each time point is conditionally independent.

4. General population survival constraint: an additional constraint was set in order to ensure the long-term predictions do not exceed survival in the general population, using general population mortality rates. The methodology of the external data is E\[\phi(t_{sub}, \phi(t_{act}, x_{sub}, x_{act}))\], with the number alive at time t and x is the number at risk at time t. The constraint is applied as follows:

\[ \frac{S_{control}(t)_{est}}{S_{control}(t)_{unknown}} = \frac{S_{unknown}(t)_{est}}{S_{unknown}(t)_{estimated}} \]

Results

Identification of relevant real-world data

Two studies with similar patient characteristics to the CheckMate 214 study were identified from the SLR of real-world data (RWD) and demonstrated the following distribution (Figure 1). Since external data was only identified for the comparator arm sunitinib, independent models for each arm were selected. Hence, the external dataset used for the independent arm was not impacted by the adjustments. Besides, since nivolumab + ipilimumab has just recently been available, there was no real-world evidence (RWE) with longer follow-up data.

As presented in Figure 1, the unadjusted models generated different long-term predictions for PFS and OS after the end of the CheckMate 214 follow-up, although the difference of AIC and BIC were sometimes small.

Figure 1: OS and PFS variations

Extrapolation of Guyot’s method

Extrapolation of PFS (Figure 2): The first step was to select the lowest AIC and BIC scores. This model was then selected for the base case using Guyot’s method.

For the extrapolation of OS, the Cox-PH PFS without external data adjustment was 20% at 5 years, while it was 17% with external data. At 5 years, the unadjusted estimate was 9%, while it was reduced to 2% including external data (Table 2).

Figure 2: Independent PFS – Extrapolations with Guyot’s method

Extrapolation of OS (Figure 3): The log-normal model mimicked AIC and BIC scores across trial arms.

The inclusion of the Vorne study using Guyot’s method had a greater impact than the KuboKawa study, mainly due to the longer follow-up, while only 3 data points were used for the KuboKawa study.

For the sunitinib arm, the predicted OS without external data adjustments on the log-normal model was 53% at 2 years, while it was 48% with external data. At 1 year, the unadjusted estimate was 27%, while it was reduced to 14% with external data (Table 2).

Figure 3: Independent OS – Extrapolations with Guyot’s method

Table 2: Predicted progression-free and overall survival with and without adjustment

<table>
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<th>Method</th>
<th>Base case survival</th>
<th>20% survival</th>
<th>50% survival</th>
<th>95% survival</th>
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<td>4.60%</td>
<td>4.60%</td>
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<td>Extrapolated (OS/MSKCC)</td>
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<td>0.00% (287)</td>
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Conclusions

NICE recommends both internal and external validations for extrapolations of long-term survival outcomes. Guyot’s method is a useful tool for extrapolations of long-term data, as it statistically adjusts long-term predictions rather than relying on a simple visual inspection of curves. Therefore, the Guyot’s method appears to be a key validation method of external validation.

Our example showed that the inclusion of external evidence using Guyot’s method had an impact on extrapolations. The impact studies, providing survival estimates over a longer time period, had a larger impact on the results.

The conclusions highlight the need to justify and list the choice of data external to adjust extrapolations.

Limitations

• NICE recommends both internal and external validations for extrapolations of long-term survival outcomes. Guyot’s method is a useful tool for extrapolations of long-term data, as it statistically adjusts long-term predictions rather than relying on a simple visual inspection of curves. Therefore, the Guyot’s method appears to be a key validation method of external validation.

• Our example showed that the inclusion of external evidence using Guyot’s method had an impact on extrapolations. The impact studies, providing survival estimates over a longer time period, had a larger impact on the results.

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References


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