Introduction

Background
Manufacturers must undertake cost-effectiveness analyses to gain approval and reimbursement of a new intervention from HTA agencies such as NICE in the UK. In oncology, the effectiveness element is mainly driven by time-to-event data collected in RCTs; particularly survival data. Given the mortality risk following a period of clinical trials, extrapolation of survival data is required to estimate long-term survival and overall survival (OS). This OS estimate is then used to inform decisions. This estimation is often a source of uncertainty in the decision-making process.

The extrapolaion decision is commonly constructed by fitting standard parametric models to Kaplan-Meier (KM) curves. As described in ‘Technical Support Document (TSD) 14’, the standard parametric models most commonly used are exponential, Weibull, gamma, and generalized gamma.

Unlike chemotherapy, immunotherapy (ITx) can both increase the immune response to cancer the work by blocking the signal that prevents T cells from attacking cancer cells. The ITx mechanism of action differs from other cancer treatments which kill cancer cells but also have the potential to damage healthy cells. ITx are well tolerated and can result in sustained survival benefits well beyond the duration of treatment.

Recent studies suggest that standard parametric distributions may not adequately model survival data for ITx and may significantly underestimate the long-term benefit. In particular, standard parametric models may be limited in their ability to capture:

- Complex non-monotonic hazard functions with multiple inflection points resulting from treatment's immunomodulatory effects
- Heterogeneity in response and OS among subgroups due to possibly of long-term survivorship and underestimated patients in phase IIIa trial.

In response, researchers have been examining alternative methods for extrapolation, which may provide more reliable survival projections for ITx therapies. However, the acceptability of these alternative methods by HTA agencies remains uncertain.

Objectives
We conducted a pragmatic review of NICE single technology appraisals (STAs) for ITx therapies, focusing on the approaches adopted for survival extrapolation. We focused on NICE STAs as the only agency that publishes the manufacturers' evidence submission, the independent citation by the Evidence Review Group (ERG) and the process through which the final decision is made.

The specific objectives of this study were:

- To identify the main limitations of standard parametric models in providing robust survival estimates for ITx therapies and to explore alternative extrapolation methods used in 53 ITx STAs.
- To understand whether the ERG considered the alternative extrapolation methods presented by the manufacturers and how these methods influenced the final decision.
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Methods

A search of the NICE website identified all the STAs published between January 2016 and December 2016.

- The inclusion criteria to select eligible STAs for the pragmatic review were the following:
- Population: all cancer-specific indications, independent of the treatment line.
- Intervention and comparators: all types of ITx therapies, e.g., immune checkpoint inhibitors (ICI), chimeric antigen receptor T-cell therapy (CAR T), adaptive T-cell transfer, interleukins, interferons, cytokine stimulating factors, monoclonal antibodies, therapeutic vaccines.
- Outcomes: non-standard parametric models for OS extrapolation, e.g., piecewise models, spline models, mixture models, response-based models, Bayesian exclusively modeling.

The following information was extracted for each selected STA:

- Details on the patient-level data and trial follow-up, the rationale provided for using an alternative extrapolation method, the type of extrapolation method implemented, the model fit to the data,
- Comments by the ERG on the alternative extrapolation approaches proposed by the manufacturer and discussion of potential differences between the manufacturer models and the ERG's preferred methods.

- Comments by the NICE committee on the alternative extrapolation approaches proposed by the manufacturer and how these methods influenced the final decision.

Results

Search and selection process
The search identified 42 STAs, of which 17 were ITx-specific and hence assessed for eligibility. While 5 of these STAs presented standard parametric distribution, 13 STAs (77%) used an alternative extrapolation method and fully met the inclusion criteria (Figure 1 and Figure 2).

The search was conducted up to 36 months, while horizon of the economic models presented in these 12 STAs ranges between 3 and 60 years.

Figure 1: Overview of 12 STAs

- Almost 95% of STAs (36/38) clearly stated that the limitation of these standard methods was the inability to capture the non-monotonic hazard function and the long-term plateau of the KM survival for ITx and hence investigated whether alternative methods were suitable to model more robust survival estimates.

Data extraction

- Manufacturers changed approach between initial and final submission in 3 STAs, switching from piecewise parametric models to non and mixture model in one response-based to piecewise parametric, resulting in 15 methods included in the review.
- The most commonly used extrapolation methods were piecewise parametric models (n=6) followed by mixture model (n=4), spline model (n=2), response-based model (n=2) and another mixture model (n=1).

- Among the 15 alternative extrapolation methods suggested by the manufacturers, 8 (53%) were considered appropriate by the ERG whereas 4 (26%) were considered appropriate by the NICE committee in the final decision (Figure 3b).

- The alternative method associated with the highest acceptability was the piecewise parametric model.

Figure 3: ERGs' and manufacturers' responses to manufacturers' alternative extrapolation methods

Conclusions

- Manufacturers of ITx therapies have a variety of approaches to address the limitations of standard parametric models in extrapolating survival for ITx therapies. 77% of STAs that are explored in this study used a mixture model for extrapolating survival for ITx therapies.
- Manufacturers presented alternative extrapolation methods. In 77% of the STAs that are explored in this study, manufacturers considered appropriate and identify the cases where the ERG would implement similar alternative extrapolation methods.
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- The pragmatic review focused on STA submissions only as no HTA authority and identified 17 conclusions employing 15 alternative approaches. Future work is recommended to determine whether the findings of this review are replicated for other HTA agencies.

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Table 1: Alternative extrapolation methods in STAs

References


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