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Modelling the survival benefit of immuno-oncologic therapy: a review of methods used in NICE single technology appraisals

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Introduction

Background

- Manufacturers must undertake cost-effectiveness analyses to gain approval and reimbursement of a new intervention from HTA authorities such as NICE in the UK.
- In oncology, the effectiveness element is mainly driven by time-to-event data collected in RCTs; particularly overall survival. Given the relatively short follow-up period of most clinical trials, extrapolating survival beyond the cut-off point of the trial is a necessary step to estimate the lifetime benefit associated with treatment. This extrapolation is often a main source of uncertainty in the decision-making process.
- The extrapolation of survival is commonly conducted by fitting standard parametric models to Kaplan Meier (KM) curves. As described in Technical Support Document (TSD) 14,[1] the standard parametric models most commonly used are: exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalized gamma.
- Unlike chemotherapy, immuno-oncologic therapies (IO) use the immune response to combat the cancer. They work by blocking the signal that prevents T-cells from attacking cancer cells. The IO mechanism of action differs from other cancer treatments which "kill" cancer cells but also have the potential to damage healthy cells. IO therapies are well tolerated and can result in sustained survival benefits well beyond the duration of treatment.[2]
- Recent studies suggest that standard parametric distributions might not adequately model survival data for IO therapies and may significantly underestimate their long-term benefits.[3-5] 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 mechanism of action.[6]
  - Heterogeneity in response and OS among subgroups due to possibility of long-term survivorship and unidentifiable positive prognostic factors.[6]
- In response, researchers have been examining alternative methods for extrapolation, which may provide more accurate survival projections for IO therapies. However, the acceptability of these alternative methods by HTA decision makers remains uncertain.

Objectives

- We conducted a pragmatic review of NICE single technology appraisals (STAs) for IO therapies, focusing on the approaches adopted for survival extrapolation. We focused on NICE STAs as this the only agency that publishes the manufacturers' evidence submission, the independent critique by the Evidence Review Group (ERG) and the process through which the final decision is made.
- The main objectives of this study were to:
  - Identify the main limitations of standard parametric models in providing robust survival estimates for IO and assess the type and frequency of alternative extrapolation methods used in IO HTA submissions.
  - Understand whether the ERG considered the alternative extrapolation methods presented by manufacturers appropriate and identify the cases where the ERG would implement similar alternative approaches or prefer the traditional parametric distributions.
  - Understand whether alternative extrapolation methods are considered appropriate by the NICE committee and to what extent using these alternative approaches, rather than the standard parametric distributions, impacted the final decision.

Methods

- A search of the NICE website identified all the STAs published between January 2018 and December 2018.

- The inclusion criteria to select eligible STAs for this pragmatic search were the following:
  - **Population**: all cancer-specific indications, independent of the treatment line.
  - **Intervention and comparators**: all types of IO therapies, e.g. immune checkpoint inhibitors (ICIs), chimeric antigen receptor T-cell therapy (CAR-T), adaptive T-cell transfers, interferons, interleukins, colony 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 averaging models.

- The following information was extracted for each selected STA:
  - Details on the patient-level data and trial follow-up, the rationale provided for use of an alternative extrapolation method, the type of extrapolation method implemented, the model fit and its results.
  - Comments by the ERG on the alternative extrapolation approaches proposed by the manufacturers and differences and/or similarities between the manufacturers' methods and the ERG's preferred methods.
  - Comments by the NICE committee on the alternative extrapolation approaches proposed by the manufacturers and how these methods influenced the final decision.

Results

Search and selection process

- The search identified 42 STAs, of which 17 were IO specific and hence assessed for eligibility. While 5 of those STAs reported standard parametric distributions, 12 STAs (77%) used an alternative extrapolation method and fully met the inclusion criteria (Figure 1 and Figure 2).
- The median follow-up of the clinical trials ranges from 9.5 months up to 36 months, while time horizon of the economic models presented in these 12 STAs ranges between 3 and 90 years.

Figure 1. PRISMA diagram

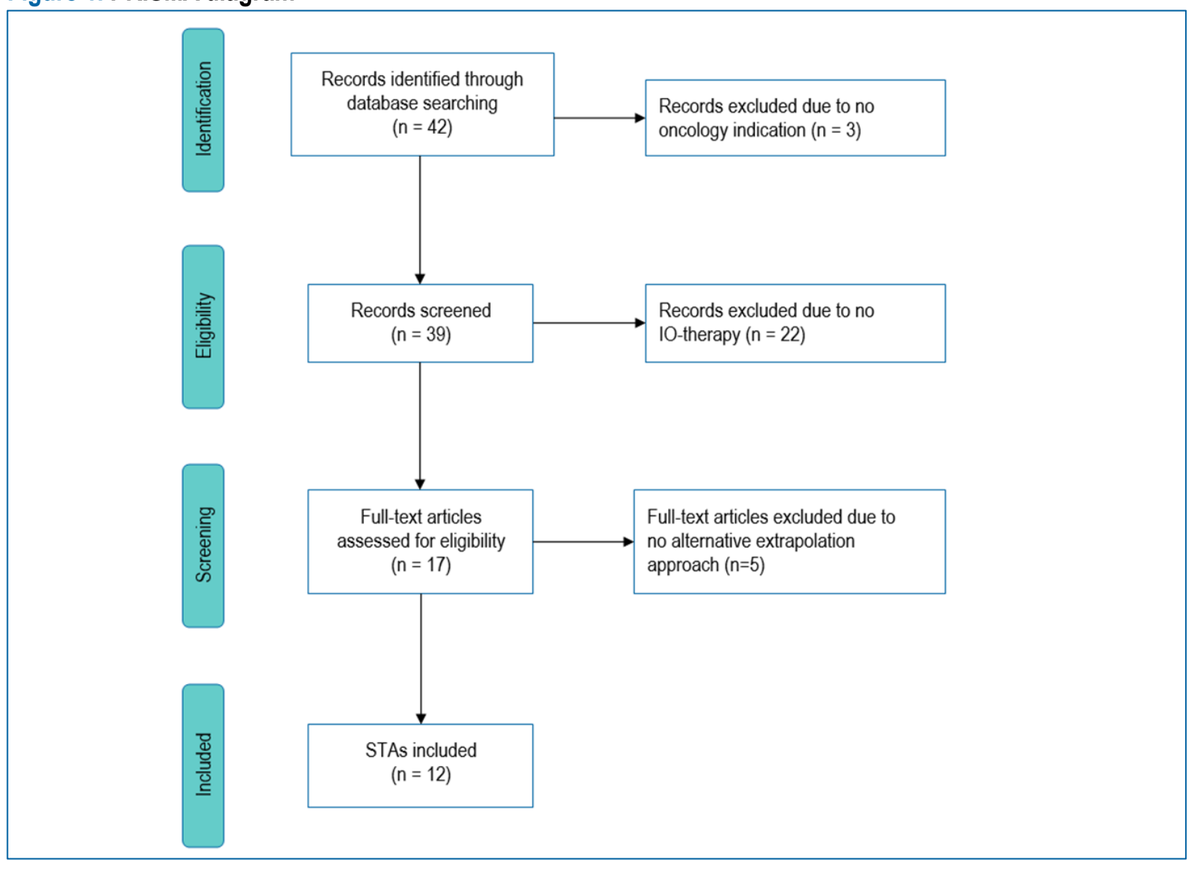
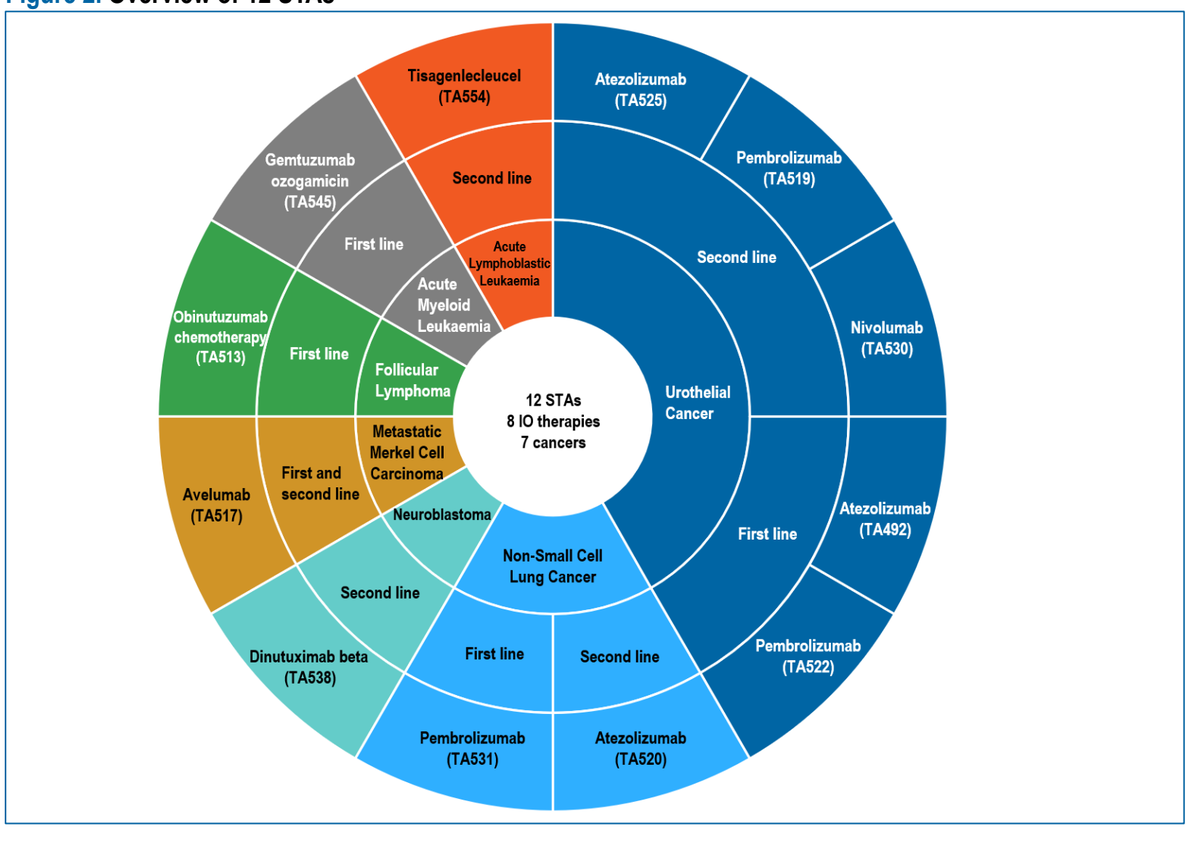


Figure 2. Overview of 12 STAs



Data extraction

- Almost 50% of STAs clearly stated that the main limitation of these standard methods was the inability to capture the non-monotonic hazard function and the long-term plateau of the KM curves for IO therapies and hence investigated whether alternative methods were suitable to provide more robust survival estimates.
- Manufacturers changed approach between initial and final submission in 3 appraisals, switching from piecewise parametric to splines and from mixture or response-based to piecewise parametric, resulting in 15 methods included in the review.
- The most commonly used alternative extrapolation methods were piecewise parametric models (n= 6), followed by mixture cure models (n = 4), spline models (n=2), response-based models (n=2) and another non-standard approach (n=1) (Table 1).
- Among the 15 alternative extrapolation methods suggested by the manufacturers, 8 (53%) were considered appropriate by the ERG (Figure 3a), while 9 (60%) were considered appropriate by the NICE committee (Figure 3b).
- The alternative method associated with the highest acceptability rate with the NICE committee was the piecewise parametric model.

Figure 3. ERG's and NICE committee's responses to manufacturers' alternative extrapolation methods

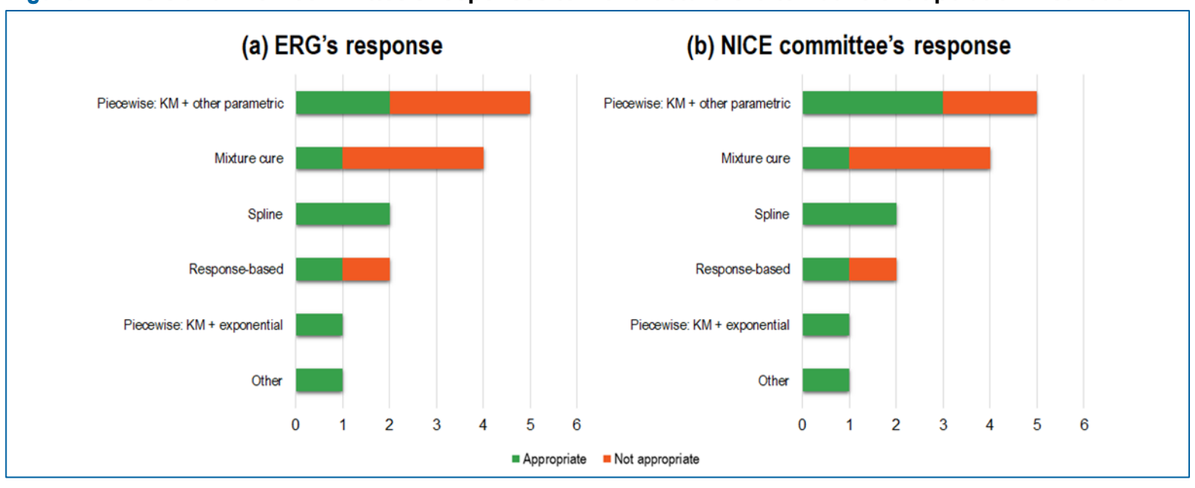


Table 1. Alternative extrapolation methods in STAs

Manufacturer's submission				ERG's response and preferred approach			NICE committee's response	
STAs	Length of trial follow-up (months)	Model approach	Final model selection	ERG's response	Model approach	Final model selection	Company's approach	ERG's approach
TA492	Cohort 1: 15 (minimum) Cohort 2: 20 (minimum)	Mixture cure	Generalized gamma	x	Piecewise parametric	KM + exponential	x	✓
TA513	34.5 (median)	Other approach	State-transition model: Modelling OS through intermediate events	✓	Other approach	Weibull + 5-year treatment effect (instead of 9-years)	✓	✓
TA517	18 (minimum)	Spline	1st line: 1-knot Odds 2nd line: 1-knot Odds	✓	Spline	1st line: 1-knot Normal 2nd line: 1-knot Odds	✓ (2nd line)	✓ (2nd line)
TA519	20.8 (median)	Piecewise parametric	KM + log-normal	✓	Piecewise parametric	KM + log-logistic	✓	✓
TA520 (initial)	OAK trial: 19 (minimum)	Initial submission: Mixture cure	Log-logistic	x	Piecewise parametric	KM + exponential	x	✓
TA520 (final)	POPLAR trial: 20 (minimum)	Final submission: Piecewise parametric	KM + log-logistic	✓	Piecewise parametric	KM + exponential	✓	✓
TA525	Single arm trial: 20 (median) RCT: 17.3 (median)	Mixture cure	Generalized gamma	x	Piecewise parametric	KM + log-logistic	x	✓
TA530 (initial)	6 (minimum)	Initial submission: Response-based landmark	Responders: KM + generalized gamma Non-responders: KM + Weibull	x	Standard parametric	Generalized gamma	x	✓
TA530 (final)		Final submission: piecewise parametric	KM + log-normal	x	Standard parametric	Generalized gamma	x	✓
TA531	11.2 (median)	Piecewise parametric	KM + exponential	✓	Piecewise parametric	KM + exponential (different switching point)	✓	✓
TA522	9.5 (median)	Piecewise parametric	KM + log-normal	x	Standard parametric	Log-normal	✓	✓
TA538 (initial)	36 (median)	Initial submission: piecewise parametric	KM + Gompertz	x	Standard parametric	Gompertz	x	✓
TA538 (final)		Final submission: 1. Standard parametric 2. Spline	1. Gompertz 2. Spline	✓	1. Standard parametric 2. Spline	1. Gompertz 2. Spline	✓	✓
TA545	36 (minimum)	Response-based mixture cure	Response: mixture cure log-normal Refractory: Gompertz	✓	Response-based mixture cure	Response: mixture cure log-normal Refractory: Gompertz	✓	✓
TA554	<36 (median)	Mixture cure	Exponential	✓	Mixture cure	Log-logistic	✓	✓

Conclusions

- Manufacturers presented NICE a variety of alternative approaches to alleviate the limitations of standard parametric methods in extrapolating survival for IO therapies. In 77 % of the STAs that are explored in this review, manufacturers utilized alternative methods for their submissions for IO therapies.
- Piecewise models, splines, response-based models and mixture cure models were the most commonly proposed alternatives by manufacturers.
- NICE committees found non-standard approaches appropriate in 60% of cases presented, indicating a willingness to take into consideration alternative survival models not reported in NICE TSD 14.[1]
- This demonstrates the need for this guidance to be updated and incorporated as part of the ongoing NICE methods review to ensure appropriate methodology is used.
- This pragmatic review focused on STA submissions only to one HTA authority and identified 17 submissions employing 15 alternative approaches. Future research is recommended to determine whether the findings of this review are replicated for other HTA agencies.

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