Exploring the Use and Acceptance of Alternative Survival Modelling Approaches for Immuno-Oncology Therapies in UK Technology Assessments

PRM109

A. Porteous,[1] N. van Hest,[1] M. Griffiths,[1] P. Morten[2]

[1]Costello Medical, London, UK; [2]Costello Medical, Cambridge, UK

Objective

- To explore the use and acceptance of alternative approaches for modelling survival in cost-effectiveness analyses submitted as part of UK health technology appraisals of immuno-oncology therapies.

Background

- Immuno-oncology (I-O) therapies have emerged in the last few years as potential treatments for a variety of cancers. Due to their novel mechanism of action, the survival profiles for these I-O therapies may be associated with a plateau, as well as evidence of a delayed effect.
- Standard parametric distributions may not adequately fit the complex survival function **(Figure 1A)**. Therefore, alternative approaches to modelling survival with I-O therapies, including mixture cure models and response-based models, have been proposed **(Figure 1B and 1C)**.[1–3]

Methods

- The National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) websites were searched in May 2018 for technology appraisals of 7 I-O therapies (atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab and tremelimumab).
- Information relating to the choice of modelling approach (including the manufacturer's rationale and appraisal committee response) was extracted from appraisals that included either mixture cure or response-based modelling (hereby referred to as 'alternative modelling approaches').

Results

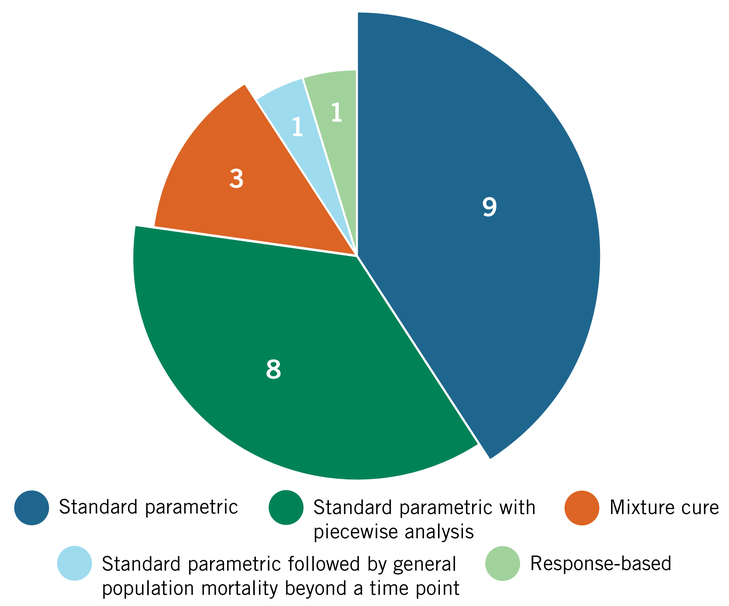
- A total of 22 NICE appraisals of I-O therapies were identified. Alternative survival modelling approaches were included in the base-case analysis of 4/22 appraisals: 3 mixture cure and 1 response-based **(Figure 2)**. A mixture cure model was included as a scenario in 1 additional appraisal.
- 1 SMC appraisal was identified that had included a response-based approach (ID 1285/18).
- A summary of the key features of these appraisals is presented in **Table 1**.
- Manufacturers justified the use of alternative modelling approaches by claiming that standard parametric distributions could not accurately reflect the survival profile of the intervention, e.g. standard approaches would fail to capture expected long-term survival benefits.
- Alternative approaches were only accepted in 2/4 appraisals (both mixture cure) and in these appraisals, the cure fraction was set to 0% in the absence of long-term data. In these cases, background mortality was incorporated in the extrapolation of the observed survival data, but otherwise the approach was similar to a standard parametric extrapolation.
- Instead, appraisal committees preferred flexible parametric or piecewise extrapolations. Key criticisms of the mixture cure and response-based approaches were that standard approaches were not shown to be inappropriate, and that sufficient evidence of a prolonged treatment effect was not provided. Where reported, median follow-up for overall survival was less than 2 years in all appraisals.

Table 1 | A summary of the appraisals that included a mixture cure or response-based modelling approach in the cost-effectiveness analysis

HTA body	Ref. number	Year published	Status	Intervention	Indication	Median follow-up for OS at the time of submission (months)	Alternative approach used	Was the modelling approach accepted?
NICE	TA520	2018	Recommended	Atezolizumab	Locally advanced or metastatic non-small-cell lung cancer after chemotherapy	21.4	Mixture cure	No
NICE	TA492	2017	Recommended within the CDF	Atezolizumab	Untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable	17.2 and 21.1	Mixture cure	Yes[a]
NICE	ID1327	Exp. 2018	Recommended	Atezolizumab	Metastatic urothelial cancer after platinum-based chemotherapy	17.2 and 21.1	Mixture cure	Yes[a]
NICE	ID995	Exp. 2018	In development	Nivolumab	Metastatic or unresectable urothelial cancer after platinum-based chemotherapy	11.5 and 9.7	Response-based	No
NICE	TA517	2018	Recommended within the CDF	Avelumab	Metastatic Merkel cell carcinoma	N/R[b]	Mixture cure (scenario analysis)	Base case (flexible splines) accepted, no comments relating to the mixture cure scenario specifically
SMC	1285/18	2018	Not recommended	Nivolumab	Locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy	11.5 and 15.2	Response-based	No

[a]Modelling approach was accepted, however the cure fraction was set to 0% in the absence of long-term data; [b]3 and 18 months minimum follow-up. CDF: Cancer Drugs Fund; Exp.: expected; HTA: health technology assessment; NICE: National Institute for Health and Care Excellence; N/R: not reported; OS: overall survival; Ref.: reference; SMC: Scottish Medicines Consortium.

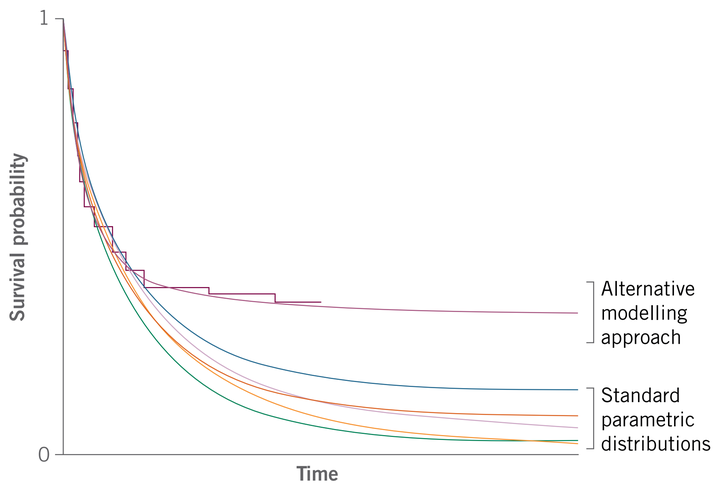
Figure 2 | Modelling approaches used in I-O therapy NICE appraisals (n=22)



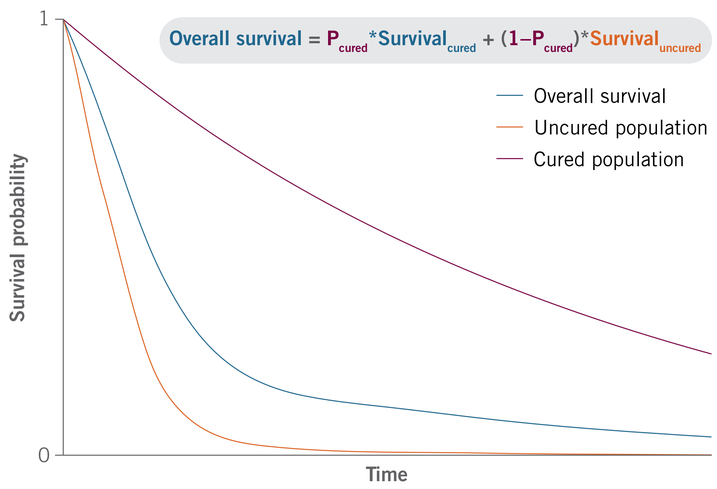
I-O: immuno-oncology; NICE: National Institute for Health and Care Excellence.

Figure 1 | Description of modelling approaches

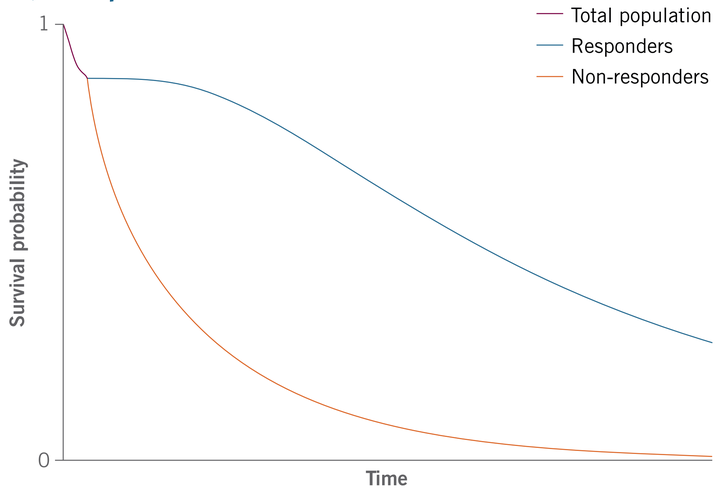
A) Standard parametric



B) Mixture cure



C) Response-based



NICE: National Institute for Health and Care Excellence.

A) Standard parametric

Standard parametric distributions, as described in the NICE Decision Support Unit Technical Support Document 14, may not adequately fit complex survival functions.

B) Mixture cure

A proportion of patients are assumed to be cured, denoted by the 'cure fraction'. 'Cured' patients are assumed to have survival equivalent to the general population, while 'uncured' patients remain subject to cancer-related risk of death. The final survival curve is weighted by the proportion of 'cured' and 'uncured' patients.

C) Response-based

A single parametric curve is fitted to the survival curve of the total population up to a chosen time point. After this time point, curves are fitted separately for 'responders' and 'non-responders', with the resulting curves weighted by the observed proportions of 'responders' and 'non-responders' at that time point.

Considerations for Manufacturers

1. Fully explore extrapolation methods as described in the NICE Decision Support Unit Technical Support Document 14 and demonstrate that standard approaches are inappropriate.[4]
2. Consider relevant sources of evidence to support the plausibility of long-term estimates, including clinical expert opinion or longer-term trial data for a similar product in the same indication (see TA414, which is not for an I-O therapy, as an example).[5]

Conclusions

- Alternative approaches to modelling survival for I-O therapies have been included in cost-effectiveness analyses submitted as part of UK technology appraisals but have not yet gained wide acceptance.
- Committees have acknowledged that these approaches are worth considering if properly evidenced. However, a lack of long-term trial data at the time of submission may limit their acceptance.
- With multiple appraisals of I-O therapies ongoing and potentially longer-term data available for I-O therapies being re-appraised following entry into the Cancer Drugs Fund, future research into the acceptance of alternative modelling approaches is warranted.

References

1. Latimer N. Empower the immune system to fight cancer. Presented at the BBS/PSI 1-Day Scientific Meeting, 15 June 2017. Basel, Switzerland; **2.** Huang M. *et al.* Value & Outcomes Spotlight 2018;4:28–30; **3.** ISPOR Glasgow (2017), Workshop 11: Determining the value of long-term outcomes associated with immuno-oncology therapies – Challenges and approaches for OS extrapolations; **4.** NICE (2011). Decision Support Unit Technical Support Document 14. Available at: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/ [Last accessed 19.09.18]; **5.** NICE (2016). TA414: Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Available at: https://www.nice.org.uk/guidance/ta414 [Last accessed 18.10.18].

Individual technology appraisals can be found on the NICE (https://www.nice.org.uk guidance) and SMC (https://www.scottishmedicines.org.uk/medicines-advice/) websites using the identifiers cited above.

Acknowledgements

The authors thank Mark Tassell, Costello Medical, for graphic design assistance.

Presented at the ISPOR 21st Annual European Congress | Barcelona, Spain | 10–14 November 2018