Survival analysis methods used in immuno-oncology NICE appraisals

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Background

- Survival analysis is often required in economic evaluations to capture survival functions seen in clinical trial data and extrapolate outcomes into the future.
- It is important to consider the hazard function during and after the trial when selecting appropriate survival models. Standard parametric models may not adequately capture complex, time-dependent hazard shapes, such as those seen with immuno-oncology treatments where patients can have a delayed response to treatment and long-term survival.[1]
- National Institute for Health and Care Excellence (NICE) Technical Support Document (TSD) 21 describes a range of more sophisticated survival modelling approaches that can be used for complex hazard functions.

Objective

- The study objective was to review the use of different survival models in immuno-oncology NICE technology appraisals (TAs) completed after the publication of TSD 21 in January 2020.
- This review examines the types of survival models used in immuno-oncology NICE submissions. It will provide insight into the types of methods used and the incorporation of more advanced statistical methods into recent NICE TAs.
- This research will determine the extent to which companies have followed the recommendations in NICE Decision Support Unit (DSU) TSD 21 and if they are incorporating more flexible survival models in their submissions to NICE. It also explores the acceptance of these more sophisticated models by evidence review groups (ERGs).

Methods

- The NICE website was searched to identify all completed TAs for immuno-oncology published from January 2020 to the end of May 2022. Information about the use of different survival models was extracted from TA documents available on the NICE website.
- NICE appraisal documents reviewed included the company submission, ERG report, appraisal consultation(s), and final appraisal determination.
- Model structure and approach to survival modelling were extracted and summarised. The data extracted included economic model structure, survival model structure, submission number, recommendation for use, survival model summary, base-case survival model, Cancer Drug Fund (CDF) review, company rationale, and ERG acceptance of the survival approach.
- Table 1 through Table 4 summarise the statistical modelling approach in completed NICE TAs for immuno-oncology after January 2020.

Results

- The searches identified 26 TAs in immuno-oncology indications: 6 immunotherapies (atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, and pembrolizumab) in different oncology indications (7 lung, 3 bladder, 3 renal, 3 skin, 3 oesophageal, 2 head and neck, 2 colorectal, 1 breast, 1 lymphatic, and 1 liver).
- Of the 26 TAs, 7 (23%) considered standard parametric survival models only, and 19 (77%) explored more sophisticated models. Flexible, spline-based models were used in 9 submissions, piecewise models were used in 13 submissions, and both flexible and piecewise models were incorporated into 1 submission.
- The ERG generally accepted the more sophisticated models when the company explored standard parametric survival extrapolations first and concluded there was a logical reason these were inappropriate. The main challenges made by the ERG's were with respect to data-uncertainty and lack of evidence.

Conclusions

- This review provides insights into the approaches used to model survival in immuno-oncology economic models developed for NICE appraisals.
- Most immuno-oncology NICE TAs completed after the publication of TSD 21 explored more sophisticated survival analysis methods when standard parametric models could not capture complex hazard functions.
- Of the 19 submissions that explored piecewise and/or flexible spline-based models, 17 were accepted by the ERG as an appropriate method to conduct survival analysis.
- The results of this study may be used to inform the survival modelling approach for future TAs.

Table 1. Standard parametric survival analysis (n = 7)

Intervention	Company rationale	ERG comments
Pembrolizumab (TA766) in adjuvant skin cancer	The base case was chosen based on statistical fit, clinical plausibility, and ERG comments.	The ERG did not have any issues with the standard parametric survival modelling but emphasised the immaturity of the survival data used and the uncertainty this creates.
Nivolumab (TA684) in adjuvant skin cancer	Goodness-of-fit statistics were the basis for the chosen base case.	The ERG accepted the standard parametric survival analysis approach and did not make any recommendations regarding the use of other methods. They did note that they would include additional censoring of the OS data in the analysis.
Atezolizumab + bevacizumab (TA666) in untreated liver cancer	The base case was informed by NICE DSU guidance, clinical plausibility, statistical fit, fit to long-term data, and visual inspection.	The ERG did not explicitly disagree with the company's choice of a standard parametric approach to survival analysis but did note multiple issues with the choices of curves.
Avelumab + axitinib (TA645) in untreated renal cancer	The base-case survival modelling choices were based on discussions with consultant oncologists from various hospitals in the United Kingdom, statistical fit (included a review of the log-cumulative hazard curves), and alignment with long-term clinical data.	The ERG accepted the standard parametric survival analysis approach and did not make any recommendations regarding the use of other methods.
Nivolumab + ipilimumab (TA780) in untreated renal cancer	There was uncertainty around the appropriateness of the proportional hazards assumption due to crossing of the log-cumulative hazard plots for PFS, OS, and TTD, so independent models were the preferred base case. Piecewise models were not considered due to the poor predictive performance of these extrapolations vs. the trial data.	The ERG disagreed with the company's choice of survival approach and preferred to fit a piecewise model, using KM data followed by an exponential curve from the point where the cumulative hazard plots showed a constant hazard rate.
Pembrolizumab + carboplatin + paclitaxel (TA770) in untreated lung cancer	Cumulative hazard and log-cumulative hazard plots visually did not appear parallel, so individual parametric distributions were fitted. The base case was chosen based on statistical fit, clinical plausibility, and ERG comments.	The ERG stated that they did not have any particular concern with the company's modelling choices but suggested that the company could have improved the submission by exploring the use of more flexible models.
Atezolizumab (TA705) in untreated lung cancer	Based on statistical fit, visual inspection, clinical expert opinion, and consistency between functions were used to model different elements of survival.	The ERG accepted the standard parametric survival analysis approach and did not make any recommendations regarding the use of other methods. They also broadly agreed with the choices of model presented but wanted more information on why the clinicians' thought curves were plausible/implausible.

KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; TTD = time-to-treatment discontinuation.

Note: All submissions contained partitioned survival models except TA766, which followed a Markov cohort structure.

Table 2. Standard parametric and piecewise survival analysis (n = 13)

Intervention	Company rationale	ERG comments
Nivolumab + ipilimumab (TA716) in pre-treated colorectal cancer	The base case was chosen based on statistical and visual best-fit.	The ERG accepted the piecewise survival analysis approach and did not make any recommendations regarding the use of other methods. However, they did reduce the length of time the KM data were applied before the parametric extrapolation began in their recommendation compared with the company base case.
Pembrolizumab + platinum- and fluoropyrimidine-based chemotherapy (TA737) in untreated oesophageal cancer	Statistical fit, logical fit (the best statistically fitting curves individually led to PFS being higher than OS), and visual fit.	The ERG observed that other possible methods may have also yielded reasonable extrapolations. They pointed out that spline-based models have been used in a range of previous NICE appraisals of immune-checkpoint inhibitor treatments. The ERG noted that while spline-based models require certain assumptions related to the number of knots and their location, piecewise models also require similar assumptions (e.g., the number and location of cut-off points). Nevertheless, the ERG was satisfied that the range of models provided by the company within its submission was sufficient to inform decision-making.
Pembrolizumab (TA772) in pre-treated lymphatic system cancer	The base-case survival models were chosen based on a combination of model fit statistics and clinical plausibility.	The ERG accepted the semi-parametric piecewise survival analysis approach and did not make any recommendations regarding the use of other methods. However, they did note that the company did not provide sensitivity analysis using alterative parametric fits for OS, so uncertainty in the analysis was not adequately addressed.
Atezolizumab (TA739) in untreated bladder cancer	To maintain consistency with the scenario that provided entry into the CDF, a KM model was used for the early part of the model with a parametric extrapolation used for the tail of the curve. Clinical expert opinion and feedback from NICE were also noted as rationale.	The ERG disagreed with the company's choice of survival approach and preferred to fit a standard parametric distribution to the whole survival curve rather than use a piecewise approach. This was because of the large uncertainty in the survival estimates.
Nivolumab (TA736) in pre-treated head and neck cancer	Clinical plausibility.	The ERG agreed that a piecewise model was the preferred method of extrapolating survival. However, they expressed concerns about the company considering only 1 distribution.
Pembrolizumab (TA709) in untreated renal cancer	Statistically reasonable, fit to external data, and visual fit.	The ERG accepted the piecewise survival analysis approach and did not make any recommendations regarding the use of other methods. The ERG considered the company's general approach to extrapolate outcomes for TTP, PFS and PPS to be appropriate but noted that the OS analyses were subject to a substantial amount of uncertainty.
Nivolumab (TA707) in pre-treated colorectal cancer	The base case was chosen based on ERG comments, visual fit and statistical fit.	The ERG believed that efficacy outcomes were measured appropriately and that the statistical methods used were broadly suitable. However, they did point out that they were not entirely convinced of the use of a piecewise model over a standard parametric approach.
Pembrolizumab (TA692) in pre-treated bladder cancer	ERG and committee feedback and clinical expert opinion.	The ERG accepted the piecewise survival analysis approach and did not make any recommendations regarding the use of other methods. However, they noted that the best time to switch to a parametric curve was uncertain and that they would begin the extrapolation earlier than in the company base case. They also stated that the extrapolation of OS was unclear and required further data collection.
Pembrolizumab + pemetrexed + platinum chemotherapy (TA683) in untreated lung cancer	Based on NICE DSU guidance, clinical plausibility, goodness-of-fit statistics, and visual inspection.	The ERG would have preferred to explore the option of using a fully parametric approach to model PFS as well as the piecewise approach adopted by the company. They explained that a fully parametric approach would avoid the need to specify a given cut-point, as the ERG did not consider the evidence presented by the company to be sufficient to justify a specific cut-point. Despite these concerns, the base-case projections provided by the company appeared to provide a reasonable fit to the Kaplan-Meier curves and therefore were considered a suitable basis to inform decision-making alongside the models that consider alternative cut points.
Pembrolizumab (TA661) in pre-treated head and neck cancer	Assessment against long-term data and statistical fit.	The ERG accepted the piecewise survival analysis approach and did not make any recommendations regarding the use of other methods. However, they did disagree with the company's chosen base-case functions.
Pembrolizumab + axitinib (TA650) in untreated renal cancer	The base case was chosen based on NICE TSD 14, long-term clinical plausibility, visual fit, and statistical fit.	The ERG accepted the piecewise survival analysis approach and did not make any recommendations regarding the use of other methods. They agreed that this was the most appropriate method given the clinical evidence but suggested that the KM data could be used for a longer time period (for PFS). The ERG concluded that the methods used to extrapolate OS and PFS for the economic model were reasonable and consistent with NICE recommended methodology, although the ERG disagrees with the choice of curves chosen for OS.
Atezolizumab + carboplatin + etoposide (TA638) in untreated lung cancer	Clinical expert opinion, statistical fit to the data, and long-term clinical plausibility.	The ERG disagreed with the company's choice of survival approach and suggested that a flexible spline-based model may be most appropriate when extrapolating long-term survival for the intervention. They considered a standard parametric model most appropriate for the comparator.
Atezolizumab + nab-paclitaxel (TA639) in untreated breast cancer	Clinical expert opinion and visual fit were the main rationales for the company's chosen base case. As there was poor visual fit to all predicted PFS curves, a piecewise model was chosen for this extrapolation.	The ERG accepted the piecewise survival analysis approach and did not make any recommendations regarding the use of other methods.

Note: All submissions contained partitioned survival models.

Table 3. Standard parametric and flexible, spline-based survival analysis (n = 5)

Intervention	Company rationale	ERG comments
Nivolumab (TA655) in pre-treated lung cancer	The base case was informed by the statistical and visual fit of the survival predictions.	The ERG accepted the survival analysis approach and did not make any recommendations regarding the use of other methods. The ERG considered the company's preferred distributions that were used to model OS and PFS were, for the purpose of decision-making, adequate.
Nivolumab (TA746) in adjuvant oesophageal cancer	Analysis was undertaken in line with the approach taken in similar appraisals of immunotherapies and as suggested in TSD 21.	The ERG accepted the survival analysis approach and did not make any recommendations regarding the use of other methods. However, they disagreed with the company's base-case choice for DFS and preferred a standard parametric curve to the chosen spline function. This was because they believed the standard parametric approach had a statistically better fit and there was no indication based on the underlying hazards or clinical plausibility.
Avelumab (TA788) in pre-treated bladder cancer	Clinical expert opinion, statistical fit to the data, and long-term clinical plausibility.	The ERG acknowledged that the submitted economic model included the functionality to fit a full range of parametric OS models and parametric and spline-based PFS models, which enabled full exploration of the uncertainty associated with the curve fitting process. The ERG did choose different survival curves in their base case than the company but noted that the company's approach to selecting survival curves was transparent and in line with NICE DSU recommendations.
Avelumab (TA691) in untreated skin cancer	The base case was primarily informed by the visual fit of the curve. The company determined this to be more important than statistical fit.	The ERG considers the methods used by the company to conduct the analyses to be broadly consistent with those recommended in NICE DSU TSD 17. They agreed that using a spline-based approach was appropriate but, given the uncertainty in the analysis, it would be most appropriate to opt for a conservative survival curve.
Nivolumab (TA713) in pre-treated lung cancer	Based on statistical fit, visual inspection, comparison with long-term data, and NICE DSU guidance.	The ERG considered that, for the purposes of decision-making, the company's preferred spline-based extrapolations were adequate.

DFS = disease-free survival.

Note: The model submitted in TA746 followed a semi-Markov structure whereas the other submissions in this table contained partitioned survival models.

Table 4. Standard and flexible parametric and piecewise survival analysis (n = 1)

Intervention	Company rationale	ERG comments
Nivolumab + ipilimumab + chemotherapy (TA724) in untreated lung cancer	The base case was chosen based on statistical fit and clinical plausibility.	Overall, the ERG was satisfied with the selection of models used in the company base-case analyses.

Note: The model submitted in TA724 was a partitioned survival model.

References

1. Quinn C, et al. J Immunother Cancer. 2020;8:e000648.

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