

Are Landmark Survival Models Accepted in National Institute for Health and Care Excellence Health Technology Evaluations?

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OBJECTIVES

- Considering recent advancements in survival modelling methodology, this research investigated the use and acceptance of landmark survival models in National Institute for Health and Care Excellence Technology Evaluations in oncology.

BACKGROUND

- Novel immuno-oncology (IO) therapies have necessitated consideration of increasingly complex survival models owing to their distinctive mechanism of action which may be associated with long-term survival and delayed onset of treatment effects.
- Standard parametric distributions may not adequately fit the resulting complex underlying hazard functions associated with such therapies. National Institute for Health and Care Excellence (NICE) Technical Support Document 21¹ (TSD21; November 2020) was developed to aid manufacturer, External Assessment Group (EAG) and Committee understanding of several flexible models that can be used to model complex hazard functions, including landmark survival models (LSMs).

What is an LSM?

- LSMs are designed to model survival based on the assumption that survival profiles may differ for patients depending on their level of response.
- Based on the assumption that treatment response is a surrogate measure for survival, LSMs use a defined landmark point at which the patients are divided into different response groups.
- Separate survival models are fitted to each response group from the landmark time point onward. Survival for the entire population is calculated by weighting the survival for each response group by the proportion of patients in each group (Figure 1).
- The survival function for two response groups (e.g. responders and non-responders) is presented in Figure 1. $S(t)$ is the survival probability at time t , I is the landmark time point, $S_{R+R-}(t|I > I)$ is the survival probability at time t given survival to time I for responders (R^+) or non-responders (R^-) (and dependent on the fitted survival model for each group), and N is the number of patients in each response category.¹

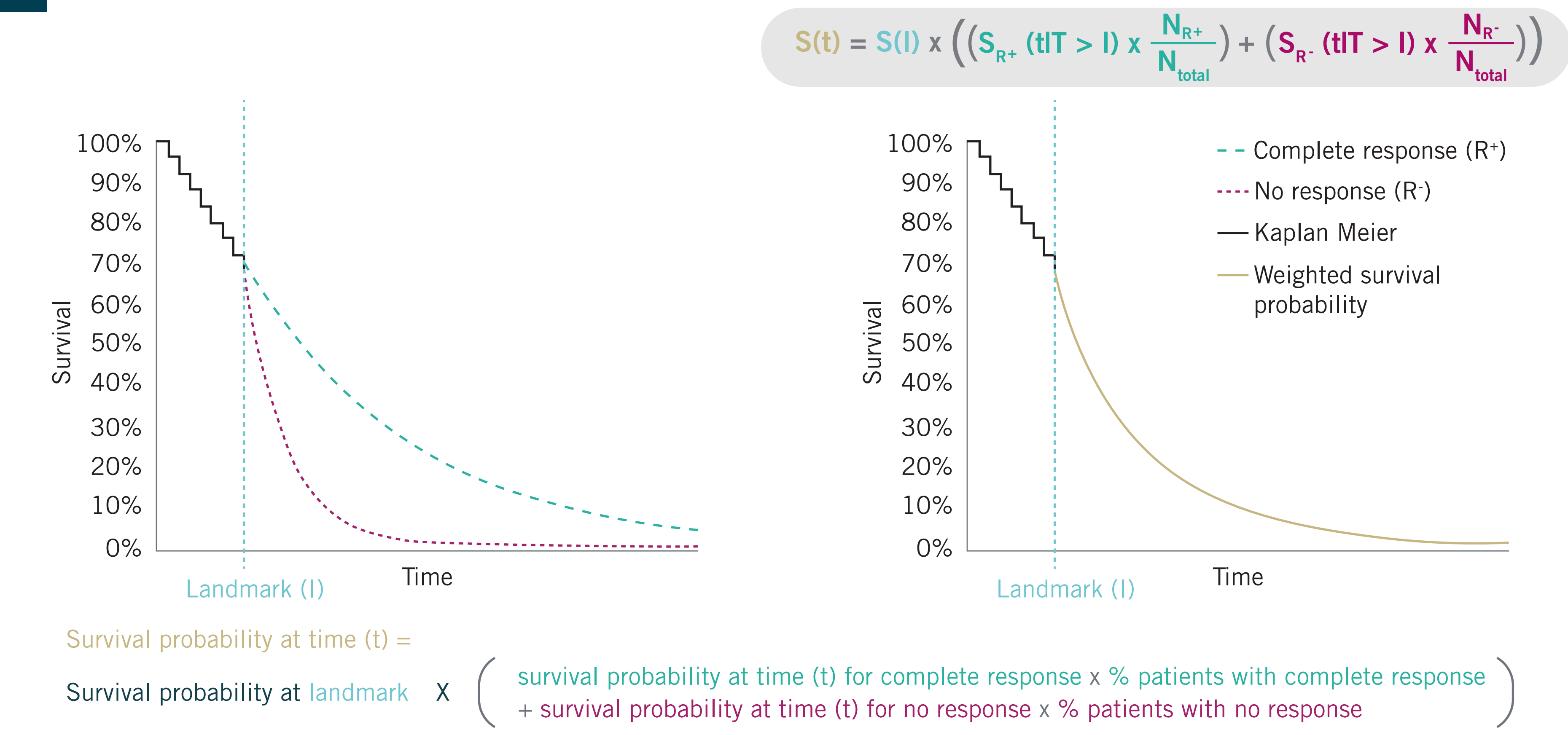
METHODS

- The NICE website was searched on 13 May 2022 for completed single and multiple technology appraisals (TAs) in all oncology indications.
- For each TA that contained an LSM stratifying patients by treatment response, information regarding survival modelling approach and EAG and Committee opinion was extracted into a prespecified extraction grid.
- Quantitative and qualitative analyses were undertaken to examine the rationale for LSM acceptance or rejection.

RESULTS

- A total of 253 TAs were reviewed. Of these, only five TAs (2%) contained LSMs, the majority of which (4/5) evaluated IO therapies and were published in the past five years (Table 1).
- In 2/5 TAs (TA763², TA530³), LSMs were used in the base case analysis within the manufacturer's cost-effectiveness model, and the manufacturer justified their use with biological rationale indicating that treatment response represented a suitable surrogate for survival. Further manufacture rationale supporting the use of LSMs was generally limited.
- The EAG suggested the use of LSMs in 2/5 cases (TA649⁴, TA421⁵). In TA421, the landmark analysis was performed by the EAG, and in TA649, the EAG suggested the potential use of an LSM as an alternative modelling approach, but this suggestion was ultimately not explored.
- In TA650⁶, LSMs were explored by the manufacturer in scenario analyses but received no further comment from the EAG or the Committee.
- The EAG disagreed with manufacturer use of LSMs in the base case in TA530 (May 2018), citing insufficient justification for complex LSMs over conventional models. The Committee shared the EAG opinion, noting it lacked evidence that LSMs were adequate for modelling long-term outcomes.
- In contrast, and though the Committee noted uncertainty, manufacturer LSMs were accepted for modelling long-term survival in TA763 (February 2022) after observing that cost-effectiveness results were similar with standard models.
- Uncertainty was the most commonly cited concern when the use of LSMs was critiqued by the EAG or the Committee, either due to immature data (TA763, TA421), the arbitrary nature of landmark time point selection (TA530) or due to the complexity introduced by the use of non-standard modelling approaches (TA763, TA649, TA530).

1 Example of a landmark survival model curve



1 A summary of TAs including LSMs

TA Ref	Date published	Status	Intervention	Indication	Use of LSM	Was the LSM accepted?
TA763	February 2022	Recommended	Daratumumab	Untreated multiple myeloma in patients eligible for stem cell transplant	Base case, scenario analyses	Yes
NICE TSD21 Published November 2020						
TA650	September 2020	Not recommended	Pembrolizumab	Untreated advanced renal cell carcinoma	Scenario analyses	N/A
TA649	September 2020	Recommended	Polatuzumab vedotin	Relapsed or refractory diffuse large B-cell lymphoma	EAG suggestion	N/A
TA530	July 2018	Not recommended	Nivolumab	Locally unresectable or metastatic urothelial cancer	Base case, scenario analyses	No
TA421	December 2016	Recommended	Everolimus	Advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy	EAG suggestion, EAG model	Yes

Abbreviations: EAG: External Assessment Group; HER2: human epidermal growth factor receptor 2; LSM: landmark survival model; N/A: not applicable; NICE: National Institute for Health and Care Excellence; TA: technology assessment; TSD: Technical Support Document.

CONCLUSIONS

- Despite advancements in survival analysis methodology, LSMs are not widely used in NICE TAs, which could reflect a lack of guidance for determining when LSMs should be considered in addition to or instead of other flexible survival models.¹
- However, the recent acceptance of LSM estimates for long-term survival in TA763 following TSD21 publication may indicate that EAGs and Committees are becoming more willing to consider LSMs a viable methodology.

Learnings for Manufacturers from Review of TAs:

- For novel IO therapies with complex hazard functions, LSMs may better reflect the underlying biology and may be preferred over standard modelling approaches, even when standard models produce similar results.
- To justify the increased complexity of LSMs, standard extrapolation methods should be shown to inadequately capture the hazard function of a technology, as per TSD14.⁷ Increased complexity should be justified by improved fit of the LSM to the observed data (past the landmark timepoint).
- The response criteria selected for defining an LSM should be a relevant surrogate for survival. Some treatments may provide benefits to both responders and non-responders, but response itself should be a treatment effect modifier for survival to warrant the use of LSMs.
- The selection of the landmark point should be optimised to best reflect the natural history of the disease and the characteristics of the treatment being modelled. As per TSD21¹ an early landmark point may miss delayed responses, whereas a late landmark point may result in a proportion of patients (especially non-responders) dying before the landmark point is reached.
- To minimise the impact of immortal time bias, responder and non-responder groups should not be modelled separately until the landmark point.

References

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