EE758

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Landmark Response Models

Nice in theory, not submitted to NICE in practice

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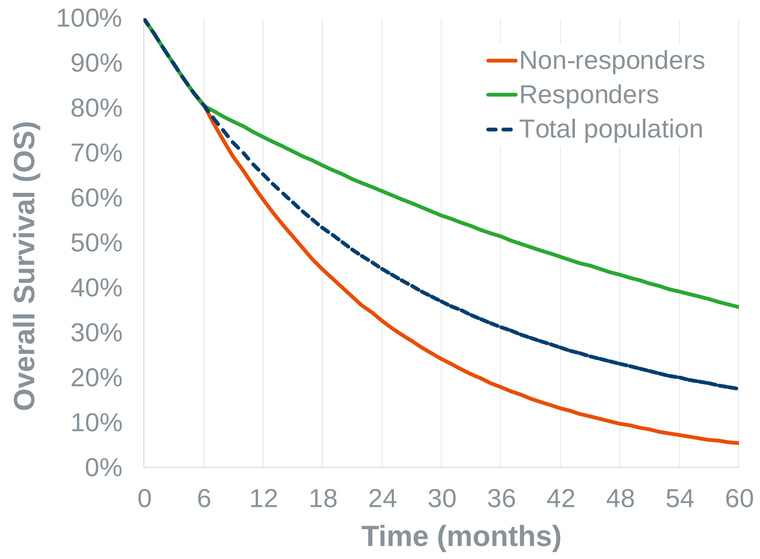
Background

- Landmark response models use a preselected "landmark" time point, after which patients are split into two or more groups according to their clinical response category (**Figure 1**). Survival for the various response subgroups is not modelled separately until the landmark point to minimize the impact of immortal time bias (i.e., responders, by definition, would have to survive to the point at which response is assessed)
- This approach has been suggested as one of several flexible techniques that may capture the distinctive characteristics of immuno-oncology and CAR-T therapies, including delayed onset of treatment effects and the potential for long-term survival, better than standard parametric survival models[1-4]. It also appeals to histology-independent / tumor-agnostic drugs, where response measures are often used as primary endpoint[5]
- While landmark response modelling may be able to represent more complex hazard functions and may better account for heterogeneity within survival data than routine parametric models, it also has some limitations[5,6]:
  - It assumes that a patient's level of response to treatment is a reliable surrogate for long-term outcomes
  - Landmark time-points may be arbitrary and may have a major impact on the results of the analysis
  - The approach does not resolve the fundamental problem of immaturity in survival endpoints
  - Further subdividing survival data into responder categories may cause the number of patients and events in certain subgroups to become small, resulting in highly uncertain survival predictions

Figure 1. Illustrative example of survival curves in a landmark response model



Objectives

- Our aim was to investigate the use and acceptance of landmark response models in oncology technology appraisals (TAs) conducted by NICE
- Gaining a better understanding how NICE responds to these analyses can offer valuable insights into improving evidence submissions and guiding future market access strategy.

Methods

- The NICE website was searched for relevant keywords (i.e., landmark, landmark responder, landmark response, landmark model, response-based) using the website's own and the Google Advanced search engines on February 28th, 2024
- Manufacturer submissions, External Assessment Group (EAG) reports, and NICE Committee documents related to retained TAs underwent two rounds of screening to identify TAs relevant to the research question

Results

- After the initial search, 41 TAs were retained. Thirty of these were excluded in a first screening, because they did not include landmark response models (n=26) or were in non-oncology indications (n=4). After further exclusion of two TAs in a second screening, **Table 1** summarizes information extracted for the remaining nine TAs
- We identified only two TAs in which manufacturers used a landmark response approach to model the impact of immunotherapy on survival endpoints directly:
  - In TA530, the EAG and NICE Committee considered that the need for a response-based approach was inadequately justified and preferred the use of standard parametric distributions
  - In TA650, the EAG and NICE Committee did not comment on the landmark response model included by the manufacturer as a scenario analysis
- Models used in several other TAs showed conceptual similarities to the landmark response approach. In TA642, TA763 and TA813, models differentiated patient outcomes in relation to a potential stem cell transplantation
- In TA763 and TA813, external data was used to justify response-based models
- In TA489 and TA644, non-responder data from single-arm studies were used as proxy for patients not receiving active treatment to generate a comparator
- In TA421, the EAG's landmark model applied a common survival trend for all patients after (rather than before) the landmark time point
- As a landmark point was not explicitly mentioned in TA644, TA813 and TA939, these models might have used a response-based approach from baseline

Table 1. NICE TAs in which the manufacturer or external assessment group developed a model using a landmark response or related approach

TA	Intervention and indication	Decision / Date	Manufacturer and NICE perspective on rationale for using landmark response approach	Landmark point
TA421	Everolimus with exemestane for treating advanced breast cancer after endocrine therapy	Recommended Dec 2016	The EAG applied the same survival trend to all patients beyond the landmark point in the landmark model it developed, based on the assumption that the intervention would extend survival until but not after disease progression.	Point at which overall survival was 62%
TA489	Vismodegib for treating basal cell carcinoma	Not recommended Nov 2017	The manufacturer's landmark approach compared non-responder data (as proxy for best supportive care) versus intent-to-treat and responder data from the same single-arm study to estimate a treatment effect. The EAG criticized this method and the uncertainty it introduced.	6 months
TA530	Nivolumab for treating locally advanced unresectable or meta-static urothelial cancer after platinum-containing chemotherapy	Not recommended Jul 2018	The manufacturer used a landmark model.to account for possible sustained and long-term treatment response. The EAG argued that the need for a response-based model was inadequately justified and preferred standard parametric distributions as per technical support documents (available at that time).	8 weeks
TA642	Gilteritinib for treating relapsed or refractory acute myeloid leukaemia	Optimised Aug 2020	The manufacturer's model showed conceptual similarities to a landmark-responder model, differentiating outcomes for patients that do versus do not undergo a hematopoietic stem-cell transplant. Whilst acknowledging this logic, the EAG criticized various structural assumptions applied in the model.	At the time of the hematopoietic stem cell transplant (fixed, but differing between comparators)
TA644	Entrectinib for treating NTRK fusion-positive solid tumours	Recommended (Cancer Drug Fund) Aug 2020	The EAG conducted a response-based exploratory analysis. Non-responder effectiveness data from a single-arm study was used as a proxy for patients not receiving active treatment and compared to a weighted average of responder and non-responder data for the active arm.	Not reported
TA650	Pembrolizumab with axitinib for untreated advanced renal cell carcinoma	Not recommended Sep 2020	The manufacturer used a landmark response model for scenario analyses with the intention to validate their base case analysis (which used routine parametric extrapolations). The EAG and NICE Committee did not comment on this landmark model in its publicly available reports.	Not reported
TA763	Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable	Recommended Feb 2022	The manufacturer leveraged pivotal trial and external data to show the relationship between response (minimal residual disease negativity at post consolidation) and long-term survival to develop a landmark response model. The EAG and NICE Committee accepted this rationale.	100 days post-autologous stem cell transplant (Mean: 37 weeks after treatment initiation)
TA813	Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors	Recommended Aug 2022	As per the EAG's suggestion, the manufacturer developed a model in which duration of progression-free survival was modelled as a function of cytogenetic and haematological response using pseudo-patient-level data digitised from an earlier NICE appraisal (TA451).	Not reported
TA885 TA939	Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer	Optimised Dec 2023	The manufacturer submitted various survival analyses, including an exploratory response-based model. The EAG did not consider the response-based analysis an appropriate substitute for imminently available OS data. A final decision was made upon availability of more mature data	Not reported

Conclusions

- Despite publication of guidance on the use of flexible models for survival analysis by the NICE Decision Support Unit in 2020[6], response-based landmark models have thus far only rarely been used in NICE TAs
- Unless a technically more complex approach can improve the fit to observed trial data (internal validity) and/or generate more plausible extrapolations (external validity), NICE appears to prefer the use of standard parametric survival models
- In solid tumors, mature data may be required to demonstrate the need for a landmark response model. In blood cancers having stem cell transplant as a subsequent treatment option, it might be easier to justify such an approach

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