BACKGROUND

The introduction of immune-oncology (IO) therapies has changed the course of treatment in oncology, offering patients the potential for long-term survival.

The therapy of choice is designed to harness the body’s own immune system to effectively re-engage the anti-tumour immune response which, unlike many other treatment options can provide continued long-term treatment effect following treatment discontinuation or dosing changes.

At the time of the National Institute for Health and Care Excellence (NICE) reimbursement submission, there is often limited long-term clinical trial data available. A major source of uncertainty in cost-effectiveness analyses is the often absence of duration and treatment effects that are seen in clinical trials.

As such, assumptions underlying long-term treatment effect on survival for IO therapies have been frequently discussed during NICE oncology technology assessment appraisals in recent years.

Specifically for indicators with a treatment-stopping rule, appropriate approaches in cost-effectiveness analyses to account for treatment-effect waning after the treatment has been suspended have been a key topic of discussion given that no formal guidance is currently available for their conduct within cost-effectiveness analyses along with currently available evidence.

OBJECTIVE

The main study objective investigated how treatment-effect waning assumptions were applied within NICE technology appraisals (TAs) of IO therapies when a treatment-stopping rule was applied.

A secondary study objective compared treatment-waning assumptions proposed during NICE health technology assessment appraisals with more mature survival data.

METHODS

Summary of appraisals

- The primary search identified 47 TAs in IO indications across 7 immunotherapies (atezolizumab, nivolumab, atezolizumab, durvalumab, pembrolizumab, and tremelimumab).
- After screening by 2 reviewers for inclusion of a treatment (effect) waning assumption and stopping rule, 12 NICE TAs were included for extraction (Table 1) which was in line with the ‘TLB best practices’

Treatment-waning assumptions

- Across all included TAs, the application of treatment-waning assumptions varied from 3 to 11 years from the start of treatment, with different waning assumptions applied with no indication being accountable for by distributions selected for survival extrapolation (TA075), gradual waning of treatment effect over a time period, or setting the hazard ratio (HR) to 1 as a specific time period (Table 2).
- The most common treatment waning assumption set the HR to 1 at a specified time point corresponding to equal hazard in both treatment arms, despite clinical input into 2 approaches (TA075 and TA428) highlighting that a more gradual waning would be more clinically plausible.

- Although the treatment-waning assumptions varied across the identified appraisals, the committee analyses were all in agreement that a 3-5-year treatment effect had been considered plausible in IO appraisals generally.

Additional follow-up

- Long-term survival data were available for 4 TAs (TA075, TA051, TA531, and TA692), which allowed for the comparison between the observed treatment effect and waning assumptions applied in each approach to IO NICE appraisals.
- When assessing the survival benefits from the more mature data (Figure 1), it is evident that the HR for majority of the follow-up period is below 1, indicating maintained treatment effect over the time period for the 4 TAs.
- However, uncertainties around the long-term treatment effects remain despite the availability of long-term follow-up data.

- Given the few events and line number of patients at risk towards the end of the follow-up period, credible intervals are wide and crossing HR = 1 for all data sets.

- Key limitations were shorter than expected duration of follow-up data which did not encompass all treatment-waning assumptions presented within the NICE TAs as well as low number of patients at risk towards the end of follow-up data.

Table 1. List of appraisals reviewed

<table>
<thead>
<tr>
<th>Appraisal code</th>
<th>Indication</th>
<th>Treatment</th>
<th>Follow-up time</th>
<th>CRD</th>
<th>NICE Technology Assessment Group (NATAG)</th>
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</thead>
<tbody>
<tr>
<td>TA075</td>
<td>pembrolizumab in adults</td>
<td>5 years</td>
<td>Equal hazard applied 3 and 5 years after stopping treatment</td>
<td>£1,091,000</td>
<td></td>
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<td>TA051</td>
<td>pembrolizumab in adults</td>
<td>5 years</td>
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<td>TA692</td>
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Table 2. Comparison of treatment-waning assumptions proposed

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</table>

Conclusions

- This review provides insights into the assumptions used to model long-term treatment effect in IO economic models developed for NICE appraisals and how these alternative assumptions fare compared with more mature data.
- This review compares common treatment-waning assumptions on treatment effects between the company, ERG, and committee with both the ERG and committee consistently arguing for shorter duration of treatment effect compared with the company.
- Key criticisms from committees across NICE TAs related to lack of availability long-term and final trial data highlighting the gap in evidence for long-term treatment effects.
- For appraisal where longer follow-up data were available, the data remain sparse and uncertain, and it is clear that uncertainties remain related to the long-term treatment effects of IOs and that data with longer follow-up are needed.
- Further analysis should inform the methodology for incorporation of treatment-effect modelling in future NICE submissions of IO therapies.
- It is imperative to periodically review this study and present updated results when extended follow-up data become available for the remaining NICE TAs identified.

ACKNOWLEDGMENTS

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REFERENCES