A Review of Treatment-Effect Waning Methods for Immuno-Oncology Therapies in National Institute for Health and Care Excellence Technology Appraisals

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BACKGROUND

- The introduction of immuno-oncology (IO) therapies has changed the course of treatment in oncology, offering patients the potential for long-term survival
- Their mechanism of action 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 disease progression[1]
- At the time of 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 often the existence and duration of treatment effect beyond that shown in clinical trials
- As such, assumptions underpinning long-term treatment effect on survival for IO therapies have been frequently discussed during NICE oncology health technology assessment appraisals in recent years
  - Specifically for indications 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 analysis
- Considering that some time has passed since the NICE appraisals of several IO therapies, data with longer follow-up, and thus information on longer-term treatment effect, have become available. In cases with longer follow-up data, this opens the possibility of reviewing how initial treatment effect assumptions align 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 appraisals with more mature survival data

METHODS

Literature review of NICE appraisals

- The NICE website (https://www.nice.org.uk) was searched to identify published NICE appraisal documents for IO therapies across different oncology indications until December 2021
  - Inclusion criteria for appraisals required the presence of a treatment-stopping rule for the treatment under investigation and a waning of treatment effect
  - The reviewed NICE appraisal documents included company submissions, evidence review group (ERG) reports, appraisal consultation(s) documents, and final appraisal determinations
- Treatment-waning information were extracted and summarised based on the following criteria:
  - Duration and application of treatment waning on primary endpoints
  - Company rationale for implementing treatment waning
  - ERG critique of approach and suggested approach
  - Impact of treatment waning on health outcomes and cost-effectiveness
  - Committee decision on treatment (effect) waning
  - Cancer Drug Fund (CDF) review (if applicable)

Literature review and assessment of follow-up survival data

- A separate targeted literature review (TLR) was conducted to identify publications with more mature survival data related to the NICE appraisal submissions identified
- The Kaplan-Meier data for primary endpoints (i.e., overall survival or progression-free survival) with longer follow-up data were digitised to produce pseudo-individual patient-level data following methods proposed by Guyot et al.[2]
- Smooth hazard plots (with credible intervals) were created based on the pseudo-individual patient-level data to allow for assessment of treatment effect with time based on the more mature survival data

RESULTS

Summary of appraisals

- The primary search identified 47 TAs in IO indications across 7 immunotherapies (atezolizumab, avelumab, blinatumomab, durvalumab, ipilimumab, nivolumab, and pembrolizumab)
  - 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 TLR best practices[3]

Treatment-waning assumptions

- Across all identified submissions, the application of treatment-waning assumptions varied from 3 to 11 years from the start of treatment, with different waning assumptions applied which included waning argued to be accounted for by distributions selected for survival extrapolation (TA737), gradual waning of treatment effect over a time period, or setting the hazard ratio (HR) to 1 at a specified timepoint (Table 2)
  - The most common treatment-waning assumption set the HR to 1 at a specified timepoint corresponding to equal hazard in both treatment arms, despite clinical input in 2 appraisals (TA737 and TA683) highlighting that a more gradual waning would be more clinically plausible
- Although the treatment-waning assumptions varied across the identified appraisals, the committee states in several of the appraisals that a 3-to-5-year treatment effect has been considered plausible in IO appraisals generally

Additional follow-up

- Long-term follow-up data were available for 4 TAs (TA578, TA692, TA531,and TA428), which allowed for the comparison between the observed treatment effect and waning assumptions applied in each respective NICE appraisal[4-7]
- When assessing the smoothed HRs 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 time period for the 4 TAs
- However, uncertainties around the long-term treatment effects remain despite the availability of longer follow-up data
- Given the few events and low number of patients at risk toward 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 capture 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

Figure 1. Smooth hazard ratios for follow-up survival data

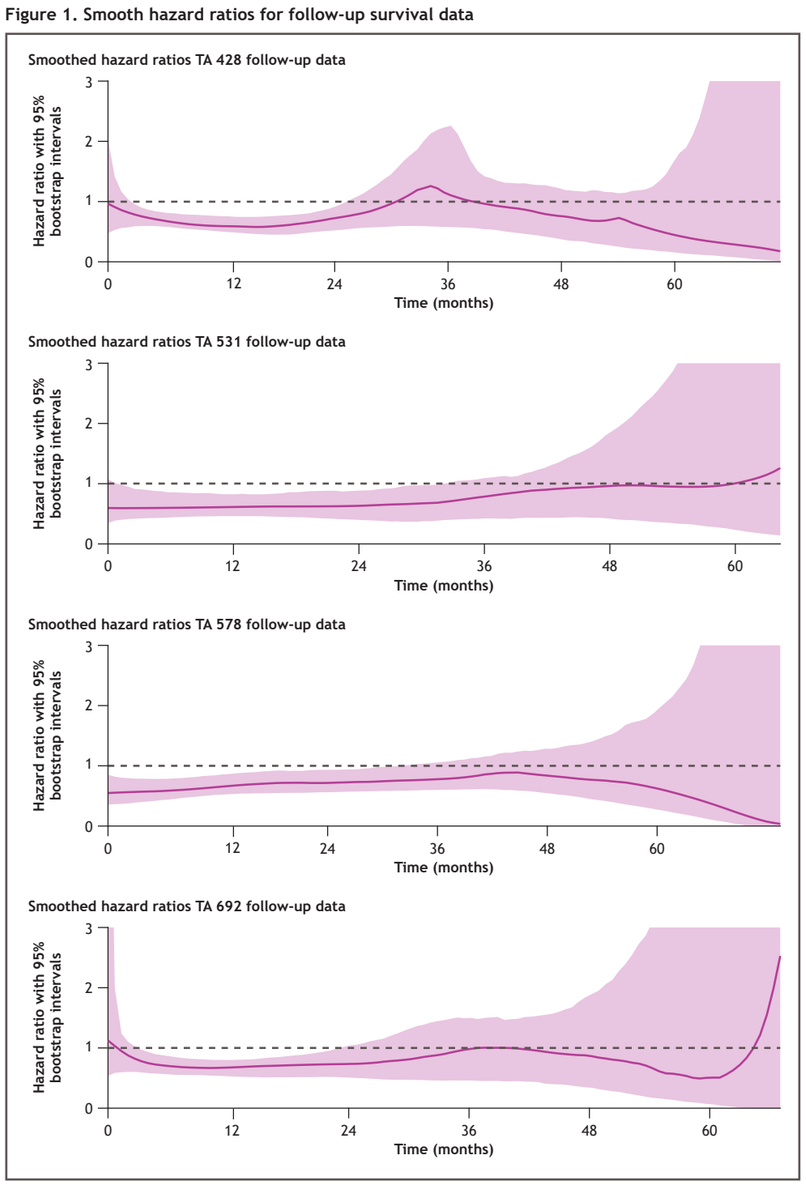

Table 1. List of appraisals reviewed

Appraisal (code)	Indication	Treatment (line of therapy)	ERG	Committee	Guidance published	Result
Nivolumab (TA724)	Lung	Untreated metastatic NSCLC in adults	CRD and CHE Technology Assessment Group	D	2021	Not recommended
Pembrolizumab (TA737)	Oesophageal	First-line treatment of patients with locally advanced unresectable or metastatic carcinoma	Peninsula Technology Assessment Group	A	2021	Recommended
Atezolizumab (TA705)	Lung	First-line treatment of adult patients with metastatic NSCLC	Aberdeen HTA Group	D	2021	Recommended
Pembrolizumab (TA770)	Lung	Untreated metastatic squamous NSCLC	School of Health and Related Research (ScHARR)	D	2019	Recommended
Pembrolizumab (TA692)	Bladder	Locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy	Warwick Evidence	D	2021	Not recommended
Pembrolizumab (TA683)	Lung	First-line treatment of metastatic non-squamous NSCLC in adults	Peninsula Technology Assessment Group (PenTAG)	NR	2021	Recommended
Pembrolizumab (TA661)	Head and neck	First-line treatment of metastatic or unresectable recurrent HNSCC in adults	Liverpool Reviews & Implementation Group (LRiG)	D	2019	Recommended
Pembrolizumab (TA650)	Renal	First-line treatment of advanced RCC in adults	Southampton Health Technology Assessments Centre (SHTAC)	C	2020	Not recommended
Durvalumab (TA578)	Lung	Locally advanced, unresectable, NSCLC after platinum-based chemoradiation	Kleijnen Systematic Reviews	D	2019	CDF entry
Blinatumomab (TA589)	Blood and bone marrow	Acute lymphoblastic leukaemia in remission with minimal residual disease activity	School of Health and Related Research (ScHARR)	C	2019	Recommended
Pembrolizumab (TA531)	Lung	Untreated PD-L1–positive, metastatic NSCLC	Liverpool Reviews and Implementation Group	D	2018	Recommended
Pembrolizumab (TA428)	Lung	PD-L1–positive NSCLC after chemotherapy	Aberdeen HTA Group	D	2017	Recommended

CDF = Cancer Drug Fund; CHE = centre for health economics; CRD = centre for reviews and dissemination; ERG = evidence review group; HNSCC = head and neck squamous cell carcinoma; HTA = health technology assessment; NR = not reported; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand-1; RCC = renal cell carcinoma.

Table 2. Assessment of treatment-waning assumptions proposed

Appraisals	Time point of stopping rule for IO treatment	Trial follow-up at time of appraisal	Waning assumption[a,b]		
			Company	ERG	Committee
Nivolumab (TA724)	2 years	Minimum duration of follow-up data: 12.7 months	Base case: A lifetime treatment effect Scenario: Equal hazard applied 3 years after stopping treatment.	Equal hazard applied 3 and 5 years after stopping treatment.	A treatment effect lasting between 3 to 5 years after the start of treatment was considered plausible.
Pembrolizumab (TA737)	2 years	Median duration of follow-up data: 12.6 months	Base case: Treatment-waning effect is reflected in the extrapolation of overall survival. Scenario: Gradual waning of hazard between the year 5-7	Gradual waning of hazard applied between the years 5-7	Scenarios presented provided plausible estimates.
Atezolizumab (TA705)	Atezolizumab; no stopping rule Pembrolizumab; 2 years	Median duration of follow-up data: 32.2 months	Atezolizumab; lifetime duration of treatment effect. Pembrolizumab; equal hazard after 5 years from the start of treatment.	Base case: Atezolizumab; lifetime duration of treatment effect. Pembrolizumab; equal hazard after 5 years from the start of treatment Scenarios: Atezolizumab; equal hazard at 8 years from the start of treatment. Pembrolizumab; equal hazard at 6, 7, and 8 years from the start of treatment.	Atezolizumab; due to lack of a stopping rule expected to have a longer treatment effect than pembrolizumab, so the committee agreed it would consider various durations of treatment-effect scenario done by the ERG for atezolizumab. Pembrolizumab; equal hazard after 5 years from the start of treatment
Pembrolizumab (TA770)	2 years	Median duration of follow-up data: 14.3 months	Base case: Equal hazard after 5 years from the start of treatment. Scenario: Equal hazard at 3 years and 10 years from start of treatment.	Equal hazard after 2, 3, or 4 years from start of treatment.	Equal hazard after 5 years from the start of treatment.
Pembrolizumab (TA692)	2 years	Median duration of follow-up data: 27.7 months	Base case: Equal hazard after 5 years from the start of treatment. Scenario: Equal hazard at 3 years and 10 years from the start of treatment.	Equal hazard after 3 years from the start of treatment.	Equal hazard after 3 years from the start of treatment.
Pembrolizumab (TA683)	2 years	Median duration of follow-up data: 10.5 months	Base case: Equal hazard after 5 years from the start of treatment. Scenario: Equal hazard after 3-year and 10-year from the start of treatment as well as a lifetime treatment effect.	Base case: Gradual linear waning of hazard from the point of stopping pembrolizumab (Year 2) until Year 5. Scenario: Gradual linear waning of hazard from the point of stopping pembrolizumab (Year 2) until year 3 and 5, and from year 3 to year 5 and 10.	Gradual linear waning of hazard from the point of stopping pembrolizumab (Year 2) until Year 5.
Pembrolizumab (TA661)	2 years	NR	Base case: Full 20 years treatment effect from starting treatment. Scenario: Equal hazard at 3 and 5 years after starting treatment.	Equal hazard after 5 years after starting treatment.	Equal hazard after 5 years after starting treatment (in line with ERG).
Pembrolizumab (TA650)	2 years	Median duration of follow-up data: 13.2 months	Base case: Lifetime treatment effect Scenario: Equal hazard at 10 years after starting treatment.	Base case: Lifetime treatment effect Scenario: Equal hazard at 5 and 10 years after stopping treatment.	Accepted a waning effect applied 5 years after stopping treatment.
Durvalumab (TA578)	1 year	Maximum duration of follow-up data: 40.5 months	Base case: Equal hazard after 10 years from start of treatment. Scenario: Equal hazard at 3 years, 5 years from the start of treatment and lifetime treatment effect.	Equal hazard after 5 years from the start of treatment.	Equal hazard after 3 to 5 years from the start of treatment. Long-term treatment effect after stopping treatment was highly uncertain
Blinatumomab (TA589)	< 1 year	18-month follow-up period	Equal hazard after 11 years from the start of treatment.	Considers reported treatment effects are likely to underestimate the associated uncertainty and should be interpreted with caution.	Concluded that the method used was appropriate but subject to uncertainty.
Pembrolizumab (TA531)	2 years	Median duration of follow-up data: 25.2 months	Base case: Lifetime treatment effect Scenario: Equal hazard after 3 years and 5 years.	NR	Equal hazard after 3 to 5 years.
Pembrolizumab (TA428)	2 years	Median duration of follow-up: 13 months	Equal hazard after 3 years, 5 years, 10 years, 15 years, and lifetime from start of treatment.	Equal hazard applied after 3 years.	Considered the company's preferred scenario of a lifetime treatment effect to be implausible, but had not been presented with any evidence on which it could agree a single clinically plausible scenario

ERG = evidence review group; IO = immuno-oncology; NR = not reported.
[a] Equal hazard suggests that a hazard ratio of 1 is applied for treatment and comparator arms at specified timepoint.
[b] Gradual waning of hazard indicates linear waning of treatment effect between specified timepoints.

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 demonstrates the implementation of inconsistent waning assumptions on treatment effect 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 critiques from committees across NICE TAs related to lack of availability long-term trial and follow-up data highlighting the uncertainties associated with duration of treatment effects
- For appraisal where longer follow-up data are available, the data remain sparse and immature, 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 analyses are required to inform the methodology for incorporation of treatment-effect modelling in future NICE submissions of IO therapies
- It is imperative to periodically revise this study and present updated results when extended follow-up data become available for the remaining NICE TAs identified

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