HTA27

A review of treatment effect waning assumptions in NICE technology appraisals of immunotherapies in early cancer settings

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Background

- TEW describes a gradual decrease in the efficacy of a treatment over time. Initially, a treatment might demonstrate significant benefits, such as improved OS during a clinical trial's follow-up period. However, these benefits might not persist in the long run.
- HTA agencies like NICE often include TEW assumptions in their preferred analyses of therapies that have a stopping rule. These assumptions are not based on empirical evidence and may reduce the likelihood of access.
- For early-stage settings, a cure point is typically imposed some time beyond the trial period, after which no (or very few) recurrences of disease occur in either treatment arm. The hazards post-cure are typically equal in both arms and therefore there is no treatment effect post a certain time point, reducing the need for additional TEW assumptions.
- However, TEW is becoming a topic of discussion with NICE in early-stage settings as EAGs and appraisal committees are now familiar with the concept of TEW in late-stage settings. This is a particular concern where there is a long gap between the end of trial follow-up and the imposition of a cure point or when a cure point is not explicitly included in an economic model for early-stage indications.
- We investigate whether the NICE appraisal committee considered TEW assumptions to be appropriate within NICE appraisals of anti-PD1/PD-L1 type IOs to treat early-stage cancers when a treatment-stopping rule was applied.

Objective

- To identify and assess early stage anti-PD1/PD-L1 type IO indications appraised by NICE, whether TEW was applied, what considerations/circumstances were listed and what methods were preferred during the appraisal process.

Methods

- A targeted literature review was undertaken in May 2024 using the NICE website.[1]
- Completed NICE TAs of anti-PD1/PD-L1 type IOs to treat resectable early-stage cancers before, during and/or after treatment with curative intent (e.g. surgery or radiotherapy) were included. No time limit was imposed.
- The NICE committee papers were reviewed to identify the company's preferred approach, the EAG's preferred approach and the committee's preferred approach to TEW.
- Two independent reviewers performed the targeted literature review in parallel. Duplicates of citations were removed.

Results

Literature review

- A total of 91 NICE TAs were identified; of those, nine met the final inclusion criteria.
- Adjuvant treatment was assessed in eight of the nine appraisals (TA766, TA830, TA837, TA746, TA817, TA876, TA823, TA684); the remaining was perioperative (TA851).
- A range of indications were assessed; melanoma was the most frequent.

Company submission

- Eight submissions included treatment stopping rules of 1 year and one submission included a stopping rule of 9 weeks[c]. These stopping rules reflected the pivotal trials.
- Seven submissions did not include TEW assumptions; of those, four provided justification (TA766, TA830, TA837, TA851) and three did not (TA746, TA817, TA876).
- Justifications included: no on-going treatment benefit modelled in progressed health states, data demonstrating sustained benefit past 1 year of treatment, lack of precedent to apply TEW in the early-stage setting and the intervention's long-acting MOA.
- One submission assumed TEW started 5 years after treatment initiation due to previous appraisal precedent in the late-stage setting (TA823).
- One submission (CDF exit) employed a PSM and used RWE to inform RFS and OS in both treatment arms after 10 years (TA684). The 10-year time point was justified by visual inspection and plateau in the KM curves and precedent from the original submission.

Clarification questions and EAG report

- In the three submissions that did not discuss TEW, the EAG reported no issue (TA746, TA817, TA876).
- In the four submissions that justified no TEW, the EAG requested further justification and scenario analysis in three (TA830, TA837, TA851). In response, the companies provided further rationale why TEW was inappropriate and declined to provide scenarios. In the fourth submission that justified no TEW (TA766), the EAG highlighted in their report that the duration of treatment effect in the submission was overestimated.
- In the submission that included TEW at 5 years, the EAG identified counterintuitive results and removed TEW assumptions from their base case (TA823).
- In the submission that included TEW at 10 years, the EAG requested the company to provide scenario analysis using earlier timepoints (2 and 3 years), which the company provided (TA684).

NICE Appraisal Committee decision

- Among the assessed FDG documents, TEW was not discussed in five of the nine appraisals (TA746, TA817, TA876, TA837, TA851); thus, the company base case assumption (no TEW) was considered accepted. All five appraisals received positive recommendations, although one was optimised (TA817).
- Of the four FDGs which reported a discussion on TEW, two acknowledged the uncertainty and considered a range of scenarios (TA684, TA830), one agreed with the EAG that TEW should be excluded (TA823) and one reported no preferred approach (TA766).
- In no appraisal did committee specify which TEW methods should be implemented in submissions of early stage anti-PD1/PD-L1 type IO indications.
- Of two submissions which included TEW assumptions in their base case, one exited the CDF (TA684) and one entered the CDF (TA823).

Table 1. List of NICE TAs reviewed

	TA684[a]	TA746	TA817	TA876	TA766[b]	TA830	TA837	TA851	TA823
Indication	Melanoma	Oesophageal/GOJ	Urothelial	NSCLC	Melanoma	RCC	Melanoma	TNBC	NSCLC
Treatment line	Adjuvant	Adjuvant	Adjuvant	Adjuvant	Adjuvant	Adjuvant	Adjuvant	Neoadjuvant + Adjuvant	Adjuvant
Publication date	Mar-21	Nov-21	Aug-22	Mar-23	Feb-22	Oct-22	Oct-22	Dec-22	Sep-22
Pivotal trial	CM-238	CM-577	CM-274	CM-816	KN-054	KN-564	KN-716	KN-522	IMpower010
Anti-PD1/PD-L1 type treatment assessed	Nivolumab	Nivolumab	Nivolumab	Nivolumab	Pembrolizumab	Pembrolizumab	Pembrolizumab	Pembrolizumab	Atezolizumab
Treatment stopping rule	1 year	1 year	1 year	9 weeks[c]	1 year	1 year	1 year	1 year	1 year
Model structure	3-state Markov and PSM[d]	3 state Markov	4 state Markov	4 state Markov	4 state Markov	4 state Markov	4 state Markov	4 state Markov	8 state Markov
Company approach to TEW	Applied at 10 years	Excluded	Excluded	Excluded	Excluded with reason	Excluded with reason	Excluded with reason	Excluded with reason	Applied at 5 years
Committee preferred approach to TEW	Considered a range of scenarios (3 to 5 years[e])	NR	NR	NR	Unclear	Considered a range of scenarios (4 to 10 years[e])	NR	NR	Exclude[f]
Recommendation	Positive (CDF exit)	Positive	Optimised recommendation	Positive	Positive (CDF exit)	Positive	Positive	Positive	Optimised recommendation for use within CDF

Figure 1. Company submissions including TEW in their base case

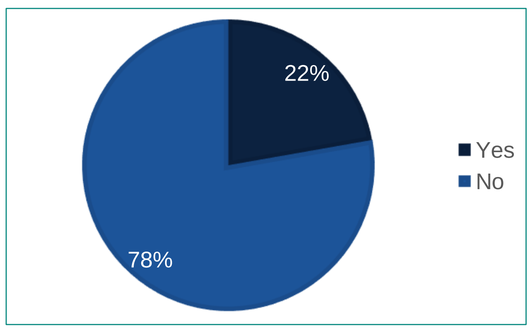


Figure 2. EAGs considering TEW assumptions at the clarification stage[g]

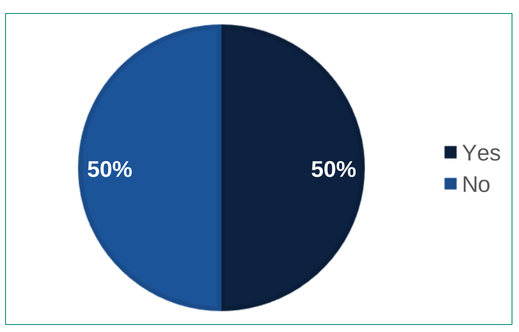
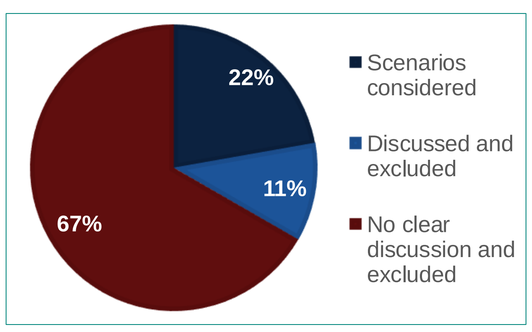


Figure 3. Committee preference



Conclusions

This review provides insights into the assumptions used to model long-term treatment effect in early stage anti-PD1/PD-L1 type IO indications appraised by NICE. These results show that TEW assumptions are not routinely imposed by NICE in the early-stage setting and may not be considered appropriate by NICE committees, depending on the context. Rather than imposing additional assumptions on the base case analysis, NICE may prefer to acknowledge the uncertainty and consider a range of plausible scenarios. Characterising the current precedent is important as precedent often informs approaches to analysis and decision-making in NICE appraisals.

[a] CDF review of TA558; [b] CDF review of TA553; [c] three three-weekly treatment cycles; [d] PSM preferred by committee; [e] years since the start of treatment; [f] including produces counterintuitive results; [g] excluding TA823

Abbreviations: CDF, Cancer Drugs Fund; CM, CheckMate; DFS, disease free survival; EAG, Evidence Assessment Group; FDG, final draft guidance; GOJ, gastroesophageal; HTA, health technology appraisal; ICER, incremental cost effectiveness ratio; IO, immunotherapy; KM, Kaplan Meier; KN, KEYNOTE; MOA, mechanism of action; NICE, National Institute for Health and Care Excellence; NR, not reported; NSCLC, non small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PSM, partitioned survival model; QR, quick response; RCC, renal cell carcinoma; RFS, recurrence free survival; RWE, real world evidence; TA, technology appraisal; TEW, treatment effect waning; TNBC, triple negative breast cancer

Disclosures

GG, IV, RW and RM are employees of Merck Sharp & Dohme (UK) Limited, London, UK.

References

1. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Available from: https://www.nice.org.uk/guidance/published

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