Exploring The Predictive Accuracy of Treatment Waning Methods: An Analysis of Pembrolizumab Across Six Oncology Indications

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Objective

To explore the accuracy of four waning methods in predicting overall survival across six oncology indications, using pembrolizumab as a case study, to assess the most appropriate waning methods for modelling long-term survival.

Background

- Approaches to account for treatment waning (i.e., the decreasing of a technology's treatment effect over time), can substantially impact long-term survival estimates for modelled treatments, with implications for health technology assessment (HTA) decision-making.[1]
- HTA bodies currently publish limited guidance on modelling treatment waning and specific methods for doing so.[1] In addition, the appropriateness of different methodologies for treatment waning has rarely been reconsidered retrospectively, once more mature, newly published overall survival (OS) data become available.
- Treatment waning is often a key uncertainty in HTA appraisals of immuno-oncology (IO) therapies in particular, as these treatments, such as pembrolizumab, may be associated with a lasting treatment effect post-discontinuation and a complex OS hazard curve.[2,3]

Methods

- A targeted search of National Institute for Health and Care Excellence (NICE) technology appraisals (TA) was conducted on 6 March 2023 to identify completed appraisals of pembrolizumab monotherapy in solid tumour indications that included a comparator arm and a two-year stopping rule for pembrolizumab. Availability of published Kaplan-Meier (KM) data for an earlier, immature data cut-off (DCO) and a later DCO in the same population were required for inclusion.
- Six eligible pembrolizumab clinical trials were identified with median follow-up of 23–28.4 months and 44.5–69.9 months for the earlier and later DCO, respectively (**Table 1**).
- Following digitisation of published OS KM curves, for early DCOs, survival for pembrolizumab and comparators was modelled via independent standard parametric extrapolation of OS data.
  - Models were selected using two methods: a) both goodness-of-fit to KM data and clinical expert estimates of plausible long-term survival from relevant NICE appraisals, or b) goodness-of-fit to KM data alone.
- Four waning methods were applied to the extrapolated data: Methods 1A and 1B assumed full treatment effect until 4 years, after which all effect was lost relative to the comparator; Methods 2A and 2B linearly waned treatment effect between 2 and 4 years (**Figure 1**).[4] The impact of applying no treatment waning was also explored.
- The stopping point of 4 years was chosen based on preliminary analyses of hazard plots; this also aligned with assumptions in previous NICE appraisals.[5–9]
- Predicted life years (LYs) were calculated from the extrapolated early DCO with each waning method and with no waning applied, over the maximum follow-up in the more mature DCO. These were compared with realised LYs over this period, which were calculated directly from long-term KM data.

Results

Extrapolations Selected Based on Clinical Feasibility and Goodness-of-Fit

- When extrapolations were selected based on clinical plausibility, all waning methods tended to underestimate LYs compared to realised LYs; the predicted LYs aligned most closely with realised LY estimates when no waning was applied (mean absolute difference: 4.6%; **Figure 2**).
- Of the waning methods, Method 1A was most often the most accurate and Method 2B was usually the least accurate compared to the realised LYs (mean absolute difference: 5.2% and 9.3%, respectively).

Extrapolations Selected Based on Goodness-of-Fit Only

- When extrapolations were selected based on statistical and visual fit to the earlier DCO KM data only, predicted LYs were no longer consistently underestimated relative to the realised LYs, and there were no apparent trends on the most accurate waning method (**Figure 3**).
- Of the waning methods, Method 1B was the most accurate on average across the trials and Method 2B was usually the least accurate compared with the realised LYs (mean absolute difference: 6.3% and 7.6%, respectively); results with no treatment waning were associated with a 7.5% mean absolute difference.

Conclusions

For OS extrapolations based on clinical plausibility as well as goodness-of-fit, applying treatment waning resulted in pessimistic predictions, with almost all predicted LYs being lower than realised LYs. This could indicate that OS extrapolations based on clinical plausibility may already inherently incorporate some degree of treatment waning effect, and applying waning on top of these extrapolations may double-count waning effects and therefore underestimate long-term survival.

When applied to survival extrapolations based on goodness-of-fit alone, treatment waning assumptions no longer consistently underestimated OS. This further suggests that survival estimations based on clinical plausibility already incorporate some expectation of treatment waning effect. Therefore, when clinical expert feedback is used to validate long-term survival extrapolations, it may be more appropriate to consider the most plausible extrapolation once waning has already been applied.

No clear conclusions on the most accurate waning methods could be drawn for OS extrapolations based on goodness-of-fit. This suggests that the most appropriate method may vary on a case-by-case basis and that alternative methods for modelling treatment waning should be explored.

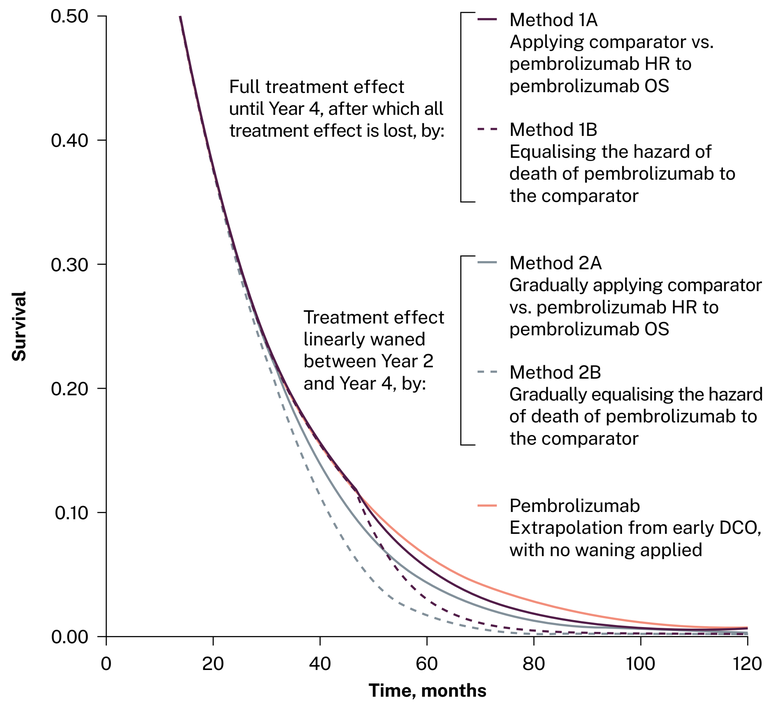
TABLE 1

List of NICE TAs and pivotal clinical trials included after a targeted search of the NICE website and relevant publications

Indication and NICE TA	Pivotal clinical trial
Pembrolizumab for advanced melanoma not previously treated with ipilimumab [TA366][5]	KEYNOTE-006
Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428][6]	KEYNOTE-010
Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531][7]	KEYNOTE-024
Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA692][8]	KEYNOTE-045
Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma [TA661][9]	KEYNOTE-048
Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [TA709][10]	KEYNOTE-177

FIGURE 1

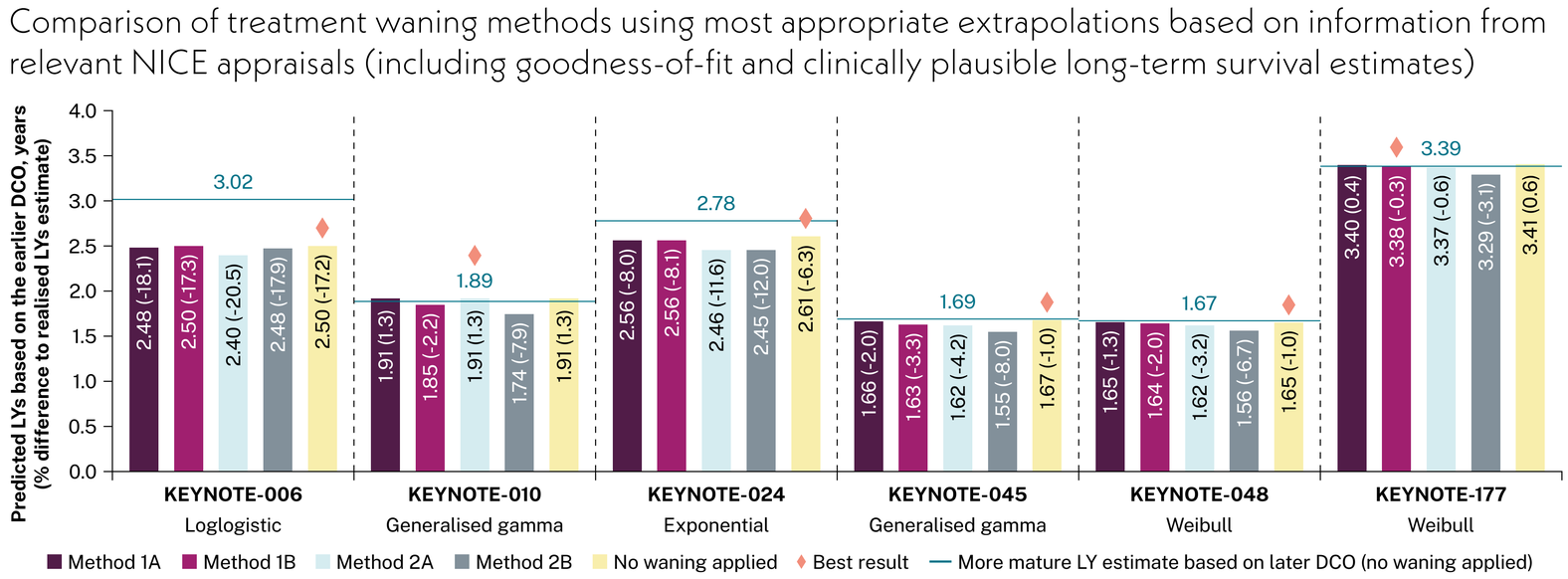
Four waning methods using KEYNOTE-048 data as an example



In this example, the Weibull extrapolation is used to model OS for pembrolizumab and the comparator, fitted to OS KM data from the earlier DCO of KEYNOTE-048. All curves start at 100% OS at Month 0, but for presentational purposes, the y-axis is only presented between 0% and 50% to focus on the part of the graph of interest.

FIGURE 2

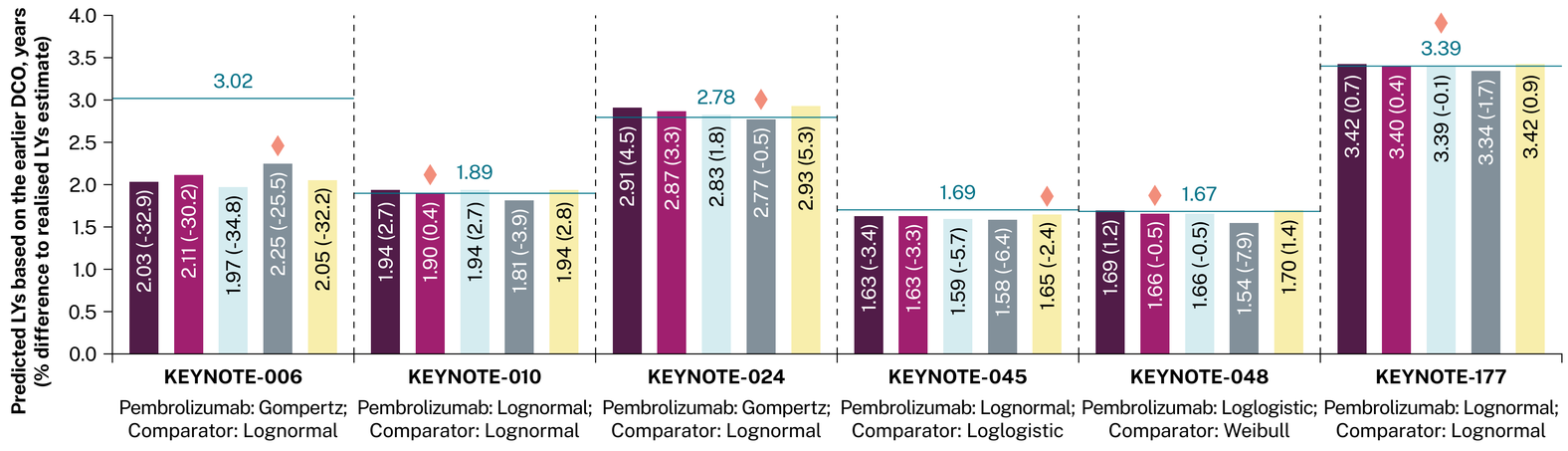
Comparison of treatment waning methods using most appropriate extrapolations based on information from relevant NICE appraisals (including goodness-of-fit and clinically plausible long-term survival estimates)



The orange diamond indicates the waning method with the smallest absolute difference compared to the realised LYs. Time horizons were aligned to the later DCOs; KEYNOTE-006: 65 months, KEYNOTE-010: 72 months; KEYNOTE-024: 66 months, KEYNOTE-045: 68 months, KEYNOTE-048: 56 months, KEYNOTE-177: 60 months. The extrapolations were chosen based on information in relevant NICE appraisals, including goodness-of-fit and the clinical plausibility of long-term extrapolations. The same extrapolation was chosen for pembrolizumab and the comparator for each trial.

FIGURE 3

Comparison of treatment waning methods using extrapolations based on statistical fit (AIC and BIC criteria) only



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Abbreviations: AIC: Akaike information criterion; **BIC:** Bayesian information criterion; **DCO:** data cut-off; **HR:** hazard ratio; **HTA:** health technology assessment; **KM:** Kaplan-Meier; **LYs:** life years; **NICE:** National Institute for Health and Care Excellence; **OS:** overall survival; **PD-L1:** programmed death ligand-1; **TA:** technology appraisal.

References: [1]Coyle D *et al*. Can J Health Technol 2023;3; [2]Marshall HT *et al*. Front. Oncol. 2018;8; [3]Ouwens MJNM *et al*. PharmacoEconomics 2019;37:1129–38; [4]Micallef J. *et al*. Presented at ISPOR, 15–18 May 2022. Washington DC, USA. MSR63; [5]National Institute for Health and Care Excellence (2015). Pembrolizumab for advanced melanoma not previously treated with ipilimumab. Available at: https://www.nice.org.uk/guidance/ta366 [Last accessed 16.10.23]; [6]National Institute for Health and Care Excellence (2017). Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. Available at: https://www.nice.org.uk/guidance/ta428 [Last accessed 16.10.23]; [7]National Institute for Health and Care Excellence (2018). Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. Available at: https://www.nice.org.uk/guidance/ta531 [Last accessed 16.10.23]; [8]National Institute for Health and Care Excellence (2021). Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. Available at: https://www.nice.org.uk/guidance/ta692 [Last accessed 16.10.23]; [9]National Institute for Health and Care Excellence (2020). Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma. Available at: https://www.nice.org.uk/guidance/ta661 [Last accessed: 16.10.23]; [10]National Institute for Health and Care Excellence (2021). Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. Available at: https://www.nice.org.uk/guidance/ta709 [Last accessed 16.10.23]. **Acknowledgements:** The authors thank Emma White, Costello Medical, for graphic design assistance. We also thank Matt Griffiths for their review and editorial assistance in the preparation of this poster.

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