Forecasting the Long-Term Treatment Effect Duration of Immuno-Oncology Therapies: An Analysis of the Predictive Accuracy of Treatment Waning Methods Applied to Pembrolizumab in Non-Small Cell Lung Cancer

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OBJECTIVES

• This research investigated the accuracy of four waning methods used in past NICE appraisals in predicting OS for IOs, using published data on pembrolizumab in people with previously untreated advanced NSCLC from KEYNOTE-024 (NCT02142738) as a case study.¹

1 Overall survival for pembrolizumab using different waning methods applied to the 25-month data cut from KEYNOTE-024

BACKGROUND

- Immuno-oncology therapies (IOs) represent a step change in the management of a variety of cancers, owing to their novel mechanism of action and potential long-term treatment effect following treatment discontinuation.
- The duration of treatment effect is a common uncertainty in health technology assessment (HTA), and choice of methodology to wane the treatment effect can have a substantial impact on estimated survival (life years [LYs]).²
- Despite this, a paucity of literature and guidance exists on appropriate methods and implementation of treatment waning in HTA.

METHODS

- Pembrolizumab and chemotherapy were modelled via independent extrapolation of Kaplan-Meier (KM) data from KEYNOTE-024.¹
- Four waning methods were applied to pembrolizumab overall survival (OS) data from the 25-month KEYNOTE-024 data cut, representing four waning methods used in past National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) (**Figure 1**)
- Two methods assumed full treatment effect for pembrolizumab versus chemotherapy until 5 years, after which all treatment effect was lost. Loss of treatment effect was modelled by:
 - Method 1: Applying the chemotherapy versus pembrolizumab hazard ratio (HR) to the pembrolizumab extrapolation (as per TA763)³
 - Method 2: Equalizing the hazard of death for pembrolizumab to that of chemotherapy (TA581)⁴
- Two other methods linearly waned treatment effect (via linear interpolation) between Year 2, to reflect the 2-year stopping rule for pembrolizumab in KEYNOTE-024, and Year 5 (as per TA779) by:⁵
 - Method 3: Gradually applying the chemotherapy versus pembrolizumab HR to the pembrolizumab extrapolation
 - Method 4: Gradually equalizing the hazard of death for pembrolizumab to that of chemotherapy
- Predicted LYs were calculated over 5.5- and 10-year time horizons, using the best-fitting curves for pembrolizumab (Gompertz) and chemotherapy (lognormal). Predicted LYs were compared with more mature LY estimates from a later data cut from KEYNOTE-024 (66-month data cut; 5.5 years),



The Gompertz extrapolation is used to model pembrolizumab OS, fitted to the OS KM data at the 25-month DCO from KEYNOTE-024. The four waning methods are then applied to the extrapolated data. **Abbreviations:** DCO: data cut-off; KM: Kaplan-Meier; OS: overall survival.

2 Overall survival for pembrolizumab based on the 66-month data cut from KEYNOTE-024 and using different waning methods applied to the 25-month data cut from KEYNOTE-024



calculated over a 5.5-year time horizon (using pembrolizumab KM data directly), and over a 10-year horizon (by extrapolating the KM data using the best-fitting curve for pembrolizumab [loglogistic] with no waning applied) (**Figure 2**).

• The accuracy of the four waning methods was also explored over a longer, 20-year time horizon as an exploratory analysis. Given the increased variation in the long-term estimates of survival between the different curve choices over a 20-year time horizon, two sets of predicted LYs and more mature LY estimates were calculated using the two best fitting curves for pembrolizumab.

RESULTS

- Over a 5.5-year horizon, predicted LYs ranged from 2.81 to 2.93 (**Table 1**). The more mature LY estimate was 2.74. All methods overestimated LYs compared to the more mature LY estimate.
- Over a 10-year horizon, predicted LYs ranged from 3.69 to 4.38 (**Table 1**). The more mature LY estimate was 3.83. Methods 1–3 overestimated LYs, whilst Method 4 underestimated LYs compared to the more mature LY estimate.
- Over a 5.5- and 10-year horizon, LYs predicted by Method 4 aligned most closely with the more mature LY estimates. More variation was observed in the LYs predicted by the different waning methods over a 10-year horizon, compared to the 5.5-year horizon.
- Over a 20-year horizon, predicted LYs ranged from 3.09 to 7.39 (**Table 2**). The more mature LY estimates were 5.19 (loglogistic) and 4.32 (Weibull). Overall, LYs predicted by Method 4 most closely aligned with the more mature LY estimates.

Predicted LYs and more mature LY estimates over a 5.5-year and 10-year horizon

Time horizon	Predicted	More mature LY estimates			
	Method 1	Method 2	Method 3	Method 4	(No waning)
5.5 years	2.93 (6.9%)	2.92 (6.7%)	2.87 (4.7%)	2.81 (2.4%)	2.74
10 years	4.38 (14.6%)	4.00 (4.7%)	4.20 (9.8%)	3.69 (–3.5%)	3.83 ^b

^aPredicted LYs calculated by extrapolating the pembrolizumab OS KM data from the 25-month DCO using the Gompertz curve and extrapolating the chemotherapy OS KM data from the 25-month DCO using the lognormal curve. ^bMore mature LY estimates over a 10-year horizon calculated by extrapolating the pembrolizumab OS KM data from the 66-month DCO using the loglogistic curve. **Abbreviations:** DCO: data cut-off; LYs: life years; KM: Kaplan-Meier; OS: overall survival. ^aAll waning methods are applied to pembrolizumab OS KM data from the 25-month DCO of KEYNOTE-024, which is extrapolated using the Gompertz curve. ^bThe loglogistic extrapolation is used to model pembrolizumab OS, fitted to the OS KM data at the 66-month DCO from KEYNOTE-024. The loglogistic extrapolation is used rather than the Weibull extrapolation for illustrative purposes. **Abbreviations:** DCO: data cut-off; KM: Kaplan-Meier; OS: overall survival.

CONCLUSIONS

- Waning based on gradually equalizing hazards (Method 4) demonstrated the greatest predictive accuracy compared to the other methods explored over the 5.5-year horizon. Over a 10-year horizon, waning based on gradually equalizing hazards (Method 4) remained the most accurate waning method.
- Over a 5.5- and 10-year horizon, waning methods that assume a full treatment effect for 5 years substantially overestimate LYs compared to the more mature LY estimates (Method 1 and Method 2). These waning methods commonly used in NICE evaluations may be overestimating the length of benefit associated with pembrolizumab. Based on this research, it is more likely that the treatment effect of pembrolizumab in NSCLC starts to wane at 2 years (immediately after discontinuation) rather than being maintained for 5 years.
- Over a longer time horizon (e.g. 10 years and most notably 20 years), there is greater uncertainty in the predicted LYs and more mature LY estimates due to the need to extrapolate beyond the trial data. As such, assessment of the predictive accuracy of different waning methods was more uncertain. Over longer time horizons, treatment waning is one of many factors, including curve selection, which contribute to the uncertainty associated with long-term OS extrapolation.

2 Predicted LYs and more mature LY estimates over a 20-year horizon

Predicted LYs extrapolation ^b	Predicted				
	Method 1	Method 2	Method 3	Method 4	More mature Ly estimates
Gompertz	7.39	5.12	6.95	4.60	5.19 [°] , 4.31 ^d
	(42.4%, 71.6%)	(-1.4%, 18.8%)	(34.0%, 61.5%)	(-11.4%, 6.8%)	
Weibull	3.30	4.22	3.09	4.25	
	(-36.4%, -23.3%)	(-18.7%, -2.0%)	(-40.4%, -28.2%)	(-18.2%, -1.4%)	

^aPercentage difference from more mature LY estimates are presented as (% difference from more mature LY estimate when extrapolating the pembrolizumab OS KM data from the 66-month DCO using the loglogistic curve, % difference from more mature LY estimate when extrapolating the pembrolizumab OS KM data from the 66-month DCO using the Weibull curve). ^bPredicted LYs calculated by extrapolating the pembrolizumab OS KM data from the 25-month DCO using the curves indicated in Table 2 and extrapolating the chemotherapy OS KM data from the 25-month DCO using the curves indicated in Table 2 and extrapolating the chemotherapy OS KM data from the 5.5-year DCO using the loglogistic curve. ^dLY estimate when extrapolating the pembrolizumab OS KM data from the 5.5-year DCO using the loglogistic curve. ^dLY estimate when extrapolating the pembrolizumab OS KM data from the 5.5-year DCO using the vertice the pembrolizumab OS KM data curve. ^dLY estimate when extrapolating the pembrolizumab OS KM data from the 5.5-year DCO using the loglogistic curve. ^dLY estimate when extrapolating the pembrolizumab OS KM data from the 5.5-year DCO using the Weibull curve. **Abbreviations:** DCO: data cut-off; LYs: life years; KM: Kaplan-Meier; OS: overall survival.

• Nevertheless, over longer time horizons, waning methods that equalize hazards demonstrated substantially greater predictive accuracy than waning by applying a HR. This is potentially because the latter methods are more susceptible to the limitations of the Cox proportional hazards assumption and applying a constant HR across the modelled time horizon.

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Acknowledgements

The authors thank Emily Fisher, Costello Medical, for graphic design assistance. We also thank Matt Griffiths, Costello Medical, for his review and editorial assistance in the preparation of this poster, and for his guidance and support of this research.



Presented at ISPOR Europe 2022 | Vienna, Austria | 6–9 November 2022

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