Duration and Timing of Treatment Waning: Determining the Start and Stop Points Using Pembrolizumab in NSCLC as a Case Study

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OBJECTIVE

- This research explored methods for determining the appropriate start and stop points of treatment waning, using pembrolizumab OS data for people with previously untreated advanced NSCLC enrolled in KEYNOTE-024 (NCT02142738) as a case study.[1]

BACKGROUND

- Treatment waning is an important source of uncertainty in health technology assessments (HTAs) when modeling long-term cost-effectiveness based on immature survival data.
- Given time horizons of economic models extend well beyond the duration of most clinical trials, assumptions around treatment waning are often based on limited evidence coupled with a lack of available guidance on how to best model the waning of treatment effect.
- Research into appropriate methods for determining the start and stop points of waning is needed to robustly incorporate treatment waning into HTAs.

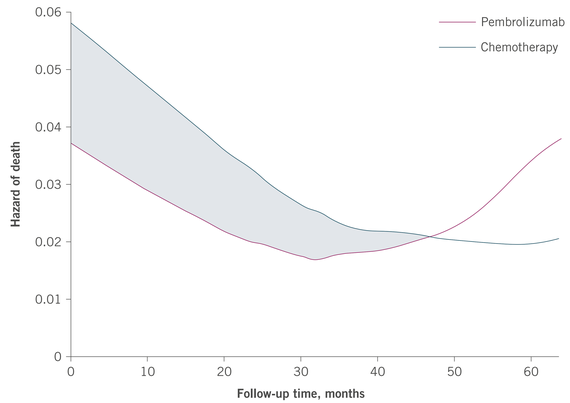
METHODS

- Using overall survival (OS) Kaplan–Meier (KM) data for pembrolizumab and chemotherapy from the 66-month data cut-off (DCO) of KEYNOTE-024, smoothed hazard plots were generated using the default Muhaz function in R.[2]
- The hazard plots were examined to determine the treatment waning start point (when the difference between the hazard of death for pembrolizumab versus chemotherapy started to decrease) and stop point (when the hazards of death equalized).
- Using an earlier, 25-month DCO of KEYNOTE-024, pembrolizumab and chemotherapy OS were modeled via independent extrapolation of KM data. Three different treatment waning assumptions were applied, and the associated predicted life years (LYs) calculated:
  - Assumption 1: Using our derived start and stop points – Assuming a full treatment effect until Month 24 (representing a round number at the end of the follow-up period) and then gradually equalizing the (via linear interpolation) hazard of death for pembrolizumab to that of chemotherapy until Month 47.
  - Assumption 2A and 2B: Using the assumptions accepted in the corresponding National Institute for Health and Care Excellence (NICE) appraisal [TA531][3] – Assuming a full treatment effect until **2A)** Month 36 or **2B)** Month 60, and thereafter all treatment effect is immediately lost.
- Predicted LYs based on the extrapolated 25-month DCO using each waning assumption were calculated over 5.5- and 10-year time horizons. The predicted LYs calculated over a 5.5-year time horizon were compared with the observed LYs from the more mature DCO (66 months [5.5 years]) from KEYNOTE-024, which required no extrapolation.[4] Predicted LYs calculated over a 10-year time horizon were compared with a more mature LY estimate based on the extrapolated 66-month DCO over the same 10-year time horizon.
- Predicted LYs based on the extrapolated 25-month DCO were calculated using the best-fitting curves for pembrolizumab (Gompertz) and chemotherapy (log-normal). For the 66-month DCO, predicted LYs were calculated over a 10-year time horizon using the best fitting curve for pembrolizumab (log-logistic), with no waning applied.[4]

RESULTS

- Based on smoothed hazard plots (**Figure 1**), the incremental hazard of death for pembrolizumab versus chemotherapy decreased (i.e. the relative survival benefit continually reduced) from Month 0.
- The hazard of death for pembrolizumab and chemotherapy equalized at Month 47. Beyond this timepoint, the hazard of death for pembrolizumab was higher than that of chemotherapy, though this may reflect the low patient numbers (n=20) at the tail-end of the pembrolizumab OS curve.
- The hazard plots for the three waning assumptions applied to the extrapolated 25-month DCO are presented in **Figure 2**.
- Over the 5.5-year time horizon, the predicted LYs using Assumption 1 were 2.76; using Assumptions 2A and 2B, the predicted LYs were 2.78 and 2.92, respectively (**Table 1**). The observed LY estimate was 2.74.[4] Based on the percentage difference from the observed LY estimate, Assumption 1 produced the closest estimate when compared with Assumptions 2A and 2B.
- Over a 10-year time horizon, predicted LYs were 3.58 for Assumption 1, 3.61 for Assumption 2A, and 4.01 for Assumption 2B (**Table 2**). The more mature LY estimate was 3.83. Assumption 2B produced the closest estimate as compared with Assumptions 1 and 2A, based on percentage difference from the more mature LY estimates.

1 Smooth hazard plots for pembrolizumab and chemotherapy based on the 66-month DCO



DCO: data cut-off.

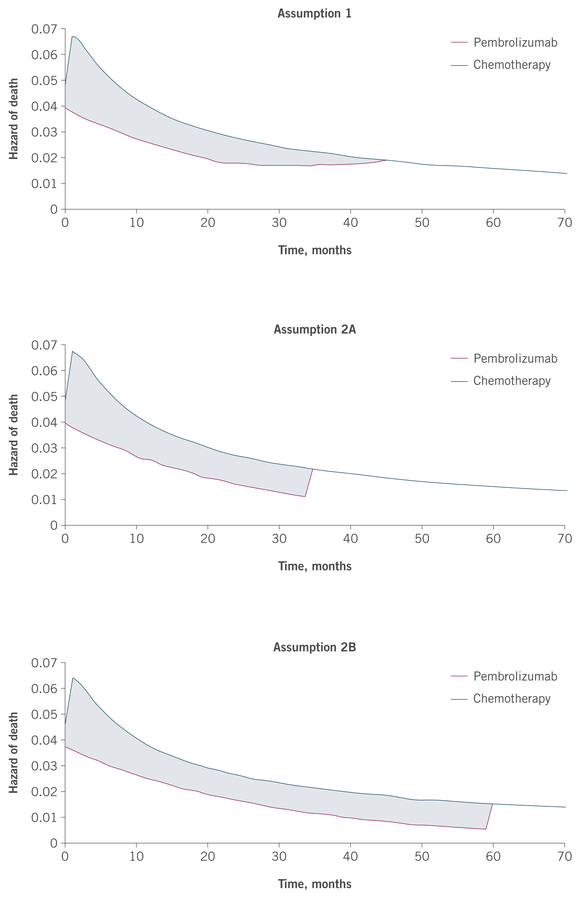
1 Predicted LYs and observed LY estimate over a 5.5-year time horizon

Treatment waning assumptions		Predicted LYs[a]	Observed LYs (no waning)	Percentage difference from observed LYs
Assumption name	Source of assumption			
Assumption 1	Hazard plot (**Figure 1**)	2.76	2.74	0.77%
Assumption 2A	TA531	2.78		1.42%
Assumption 2B	TA531	2.92		6.72%

[a]Predicted LYs calculated by extrapolating the pembrolizumab OS KM data from the 25-month DCO using the Gompertz curve.

DCO: data cut-off; **KM:** Kaplan-Meier; **LY:** life years; **OS:** overall survival.

2 Hazard plots for pembrolizumab and chemotherapy with the three waning timing assumptions applied to the extrapolated 25-month DCO



[a]Pembrolizumab is extrapolated using the Gompertz curve. [b]Chemotherapy is extrapolated using the log-logistic curve.

DCO: data cut-off.

2 Predicted LYs and more mature LY estimate over a 10-year time horizon

Treatment waning assumptions		Predicted LYs[a]	More mature LY estimate (no waning)	Percentage difference from more mature LY estimate
Assumption name	Source of assumption			
Assumption 1	Hazard plot (**Figure 1**)	3.58	3.83	–6.42%
Assumption 2A	TA531	3.61		–5.74%
Assumption 2B	TA531	4.01		4.57%

[a]More mature LY estimates over a 10-year horizon calculated by extrapolating the pembrolizumab OS KM data from the 66-month DCO using the log-logistic curve.

DCO: data cut-off; **LY:** life years; **KM:** Kaplan-Meier; **OS:** overall survival.

CONCLUSIONS

- Based on assessment of a longer-term (66-month) DCO of KEYNOTE-024, it is most accurate to apply treatment waning immediately at the end of the observed data period until Month 47 when extrapolating from the earlier DCO of KEYNOTE-024. There was no evidence to support maintaining the full treatment effect into the extrapolation period.
- Over the 5.5-year time horizon, Assumption 1 produces the closest LY estimate relative to the observed LYs, followed by Assumption 2A. Assuming full treatment effect until Month 60 (Assumption 2B) appears to overestimate the observed LYs.
- Over a longer time-horizon (10-year), the analysis is inherently more uncertain, due to the influence of factors on long-term OS extrapolation, such as curve selection. As such, it is more difficult to draw conclusions on the appropriateness of different waning assumptions.
- Further research is required to elucidate any trends that can be used to inform improved waning assumptions when extrapolating immature data.

References

1. ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer (MK-3475-024/KEYNOTE-024). Available at: https://www.clinicaltrials.gov/ct2/show/NCT02142738 [Last accessed 16 March 2023]; **2.** Ouwens MJNM *et al*. 2019;37(9):1129–38; **3.** Harrington HE *et al*. (2022). MSR34, 2022–11, ISPOR Europe, Vienna, Austria; **4.** National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531]. Available at: https://www.nice.org.uk/guidance/ta531 [Last accessed 16 March 2023].

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