When Does a Treatment Effect Really Stop?
Exploration of Different Methods for Modelling Treatment Waning

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OBJECTIVES

- We aimed to investigate the implications of different waning methods used in past NICE appraisals for predicted survival, using published CheckMate-057 (NCT01673867) data on nivolumab versus docetaxel in metastatic NSCLC, as a case study.[1]

BACKGROUND

- Novel treatments, such as immune-oncology therapies (IOs), have emerged in recent years as potential treatments for a variety of cancers. Due to their mechanism of action, these treatments may offer a long-term treatment effect following treatment discontinuation.[2]
- Treatment effect duration is a common uncertainty in health technology assessment (HTA) and treatment effect waning is frequently considered in cost-effectiveness analyses.
- There is limited guidance on treatment waning and there is inconsistency in HTA about how it is implemented. Treatment waning methodology is an area of uncertainty in cost-effectiveness analyses in HTA submissions.
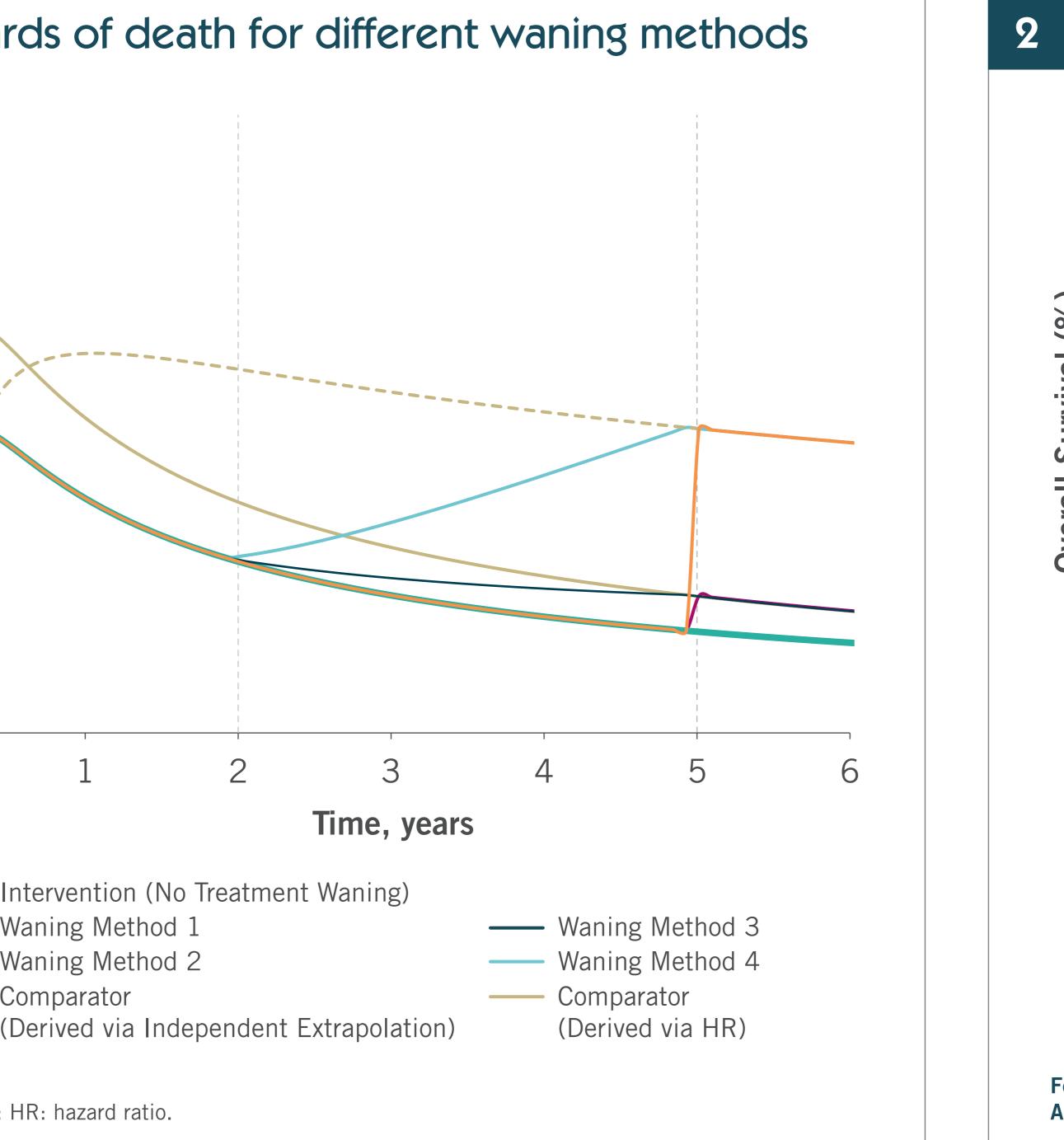
METHODS

- Nivolumab and docetaxel were modelled via independent extrapolation of Kaplan-Meier (KM) data from the CheckMate-057 trial in metastatic non-small cell lung cancer (NSCLC).[1] We also explored modelling docetaxel by applying a cox-regression model hazard ratio (HR) to the nivolumab extrapolation.
- Four treatment waning methods used in past National Institute for Health and Care Excellence (NICE) technology appraisals were applied to nivolumab's overall survival (OS) extrapolation, representing an exemplary treatment effect after discontinuation at Year 2 (reflecting the common stopping rule for IOs) that is maintained until Year 5 **(Figure 1)**. Two methods assumed a full treatment effect until Year 5. From Year 5, all treatment effect was lost, modelled by:
  – **Method 1)** Applying the HR for docetaxel versus nivolumab to the nivolumab extrapolation (as per NICE TA763[3])
  – **Method 2)** Equalizing nivolumab's hazard of death to docetaxel's hazard of death (as per NICE TA581[4])
- Two other methods linearly waned the treatment effect between Year 2 and Year 5 by:
  – **Method 3)** Gradually applying the HR for docetaxel versus nivolumab to the nivolumab extrapolation (as per NICE TA779[5])
  – **Method 4)** Gradually equalizing nivolumab's hazard of death to docetaxel's hazard of death (as per NICE TA779[5])
- Incremental life years (LYs) were calculated over a lifetime horizon (approximately 19 years) for the three statistically best fitting nivolumab and docetaxel curve choices (nivolumab: lognormal, generalised gamma and exponential; docetaxel: Weibull, log-logistic and generalised gamma; **Figure 2**).
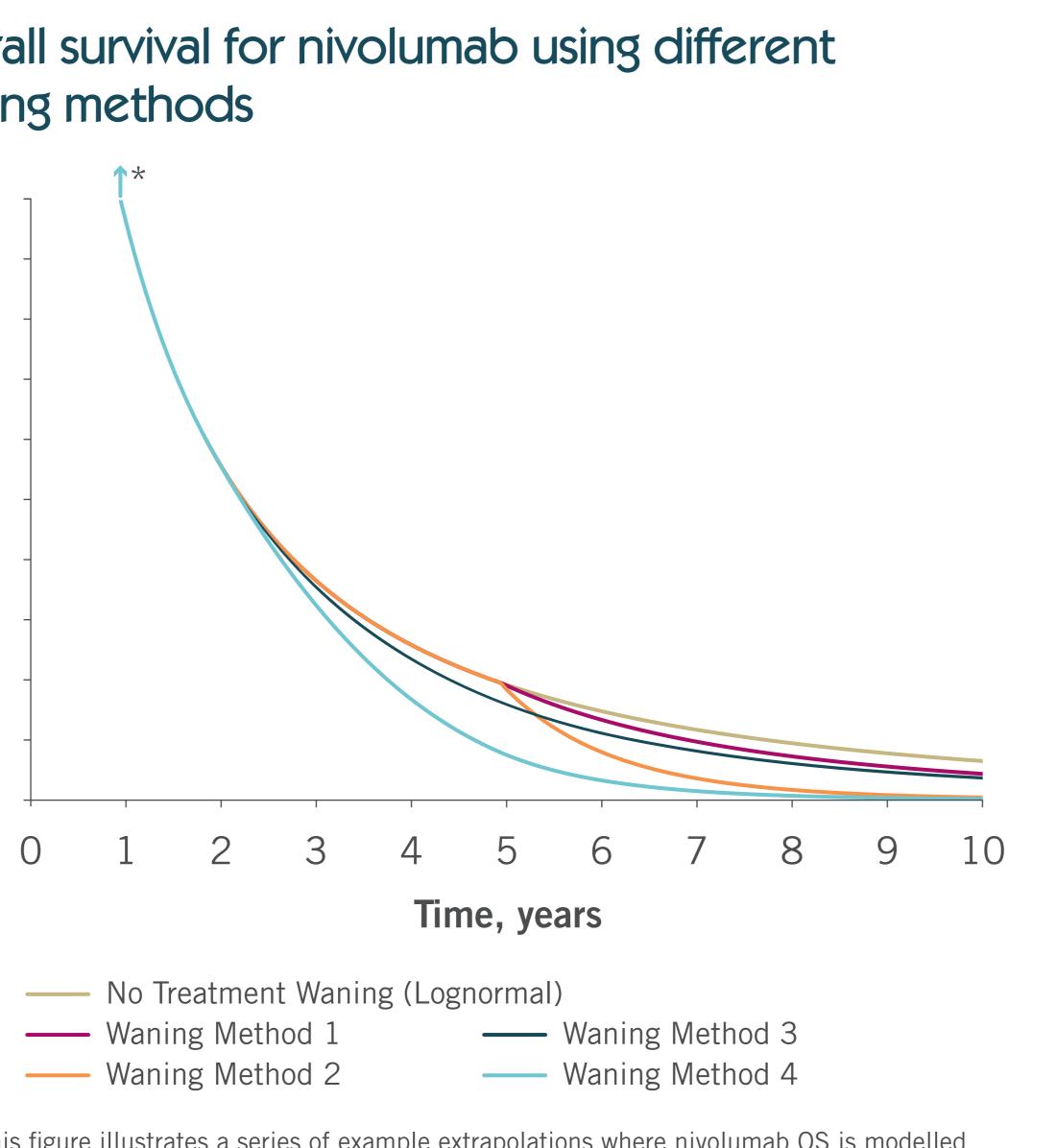
1 | Hazards of death for different waning methods

Abbreviations: HR: hazard ratio.

Legend:
- Intervention (No Treatment Waning)
- Waning Method 1
- Waning Method 2
- Comparator (Derived via Independent Extrapolation)
- Waning Method 3
- Waning Method 4
- Comparator (Derived via HR)

3 | Overall survival for nivolumab using different waning methods
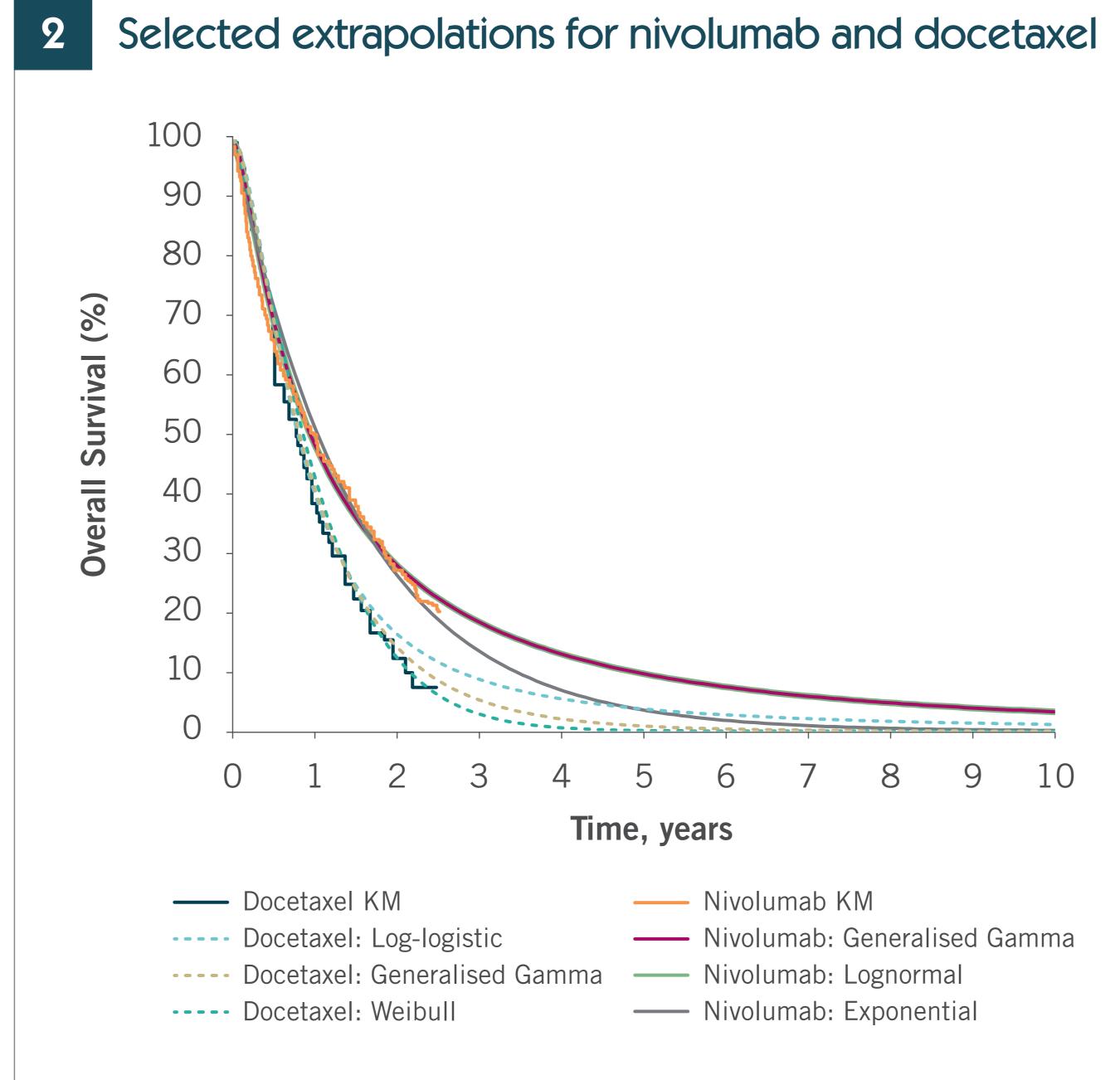
Footnotes: This figure illustrates a series of example extrapolations where nivolumab OS is modelled using the lognormal extrapolation, and treatment waning is based on the docetaxel OS profile using the Weibull extrapolation. *All curves start at 100% overall survival at Year 0, but for presentational purposes, the y-axis is only presented between 0% and 50% to focus on the part of the graph of interest.
Abbreviations: OS: overall survival.

Legend:
- No Treatment Waning (Lognormal)
- Waning Method 1
- Waning Method 2
- Waning Method 3
- Waning Method 4

2 | Selected extrapolations for nivolumab and docetaxel

Footnote: The extrapolations in this figure are presented prior to the application of treatment waning.
Abbreviations: KM: Kaplan-Meier.

Legend:
- Docetaxel KM
- Docetaxel: Log-logistic
- Docetaxel: Generalised Gamma
- Docetaxel: Weibull
- Nivolumab KM
- Nivolumab: Generalised Gamma
- Nivolumab: Lognormal
- Nivolumab: Exponential

RESULTS

- When both treatments were modelled via independent extrapolation, the incremental LYs between nivolumab and docetaxel varied substantially across the waning scenarios and curve choices. The range of incremental LYs across the four waning methods for a given set of curve choices ranged from 0.04 LYs (nivolumab: exponential; docetaxel: generalised gamma) to 0.47 LYs (nivolumab: lognormal; docetaxel: Weibull; **Figure 3** and **Table 1**).
- Varying the nivolumab curve choice from the best fitting lognormal to the generalised gamma curve resulted in negligible change in incremental life years across all methods. The mean changes in incremental LYs when varying the nivolumab curve from lognormal to exponential were equal to 0.42 LYs (Method 1), 0.25 LYs (Method 2), 0.38 LYs (Method 3) and 0.11 LYs (Method 4).
- Using the exponential curve to model nivolumab resulted in the least variation in incremental LYs when varying the waning method, compared to the lognormal or generalised gamma curves, aside from when the log-logistic curve was chosen to model docetaxel.
- When docetaxel was derived by applying a HR to nivolumab's extrapolation, there were minimal differences in incremental LYs between waning methods, and any changes to results were driven by the nivolumab curve choice. **(Table 1)**.

1 | Incremental LYs based on a range of curve choices and waning methods

Docetaxel curve choice*	Nivolumab curve choice*	Waning method 1	Waning method 2	Waning method 3	Waning method 4	Range across waning method
Weibull	Lognormal	0.85	0.57	0.77	0.37	0.47
	Generalised gamma	0.85	0.57	0.77	0.37	0.47
	Exponential	0.43	0.41	0.40	0.33	0.10
Log-logistic	Lognormal	0.55	0.63	0.47	0.54	0.16
	Generalised gamma	0.55	0.63	0.47	0.54	0.16
	Exponential	0.13	0.24	0.09	0.33	0.23
Generalised gamma	Lognormal	0.79	0.58	0.72	0.42	0.37
	Generalised gamma	0.79	0.58	0.72	0.42	0.37
	Exponential	0.38	0.38	0.34	0.34	0.04
HR applied to nivolumab	Lognormal	0.59	0.59	0.51	0.51	0.08
	Generalised gamma	0.59	0.59	0.51	0.51	0.08
	Exponential	0.38	0.38	0.34	0.34	0.04

Footnotes: Results for the nivolumab lognormal and generalised gamma curves vary when LY estimates to more decimal places are used. *Incremental LYs are presented for the three best fitting curves for nivolumab and docetaxel.
Abbreviations: LYs: life years.

CONCLUSIONS

- In our research, the choice of waning method is most influential when both the intervention and comparator are modelled via independent extrapolation; in this situation, the choice between applying a HR versus equalization of hazards, and between immediate versus gradual waning, can both have substantial impact on the results.
- When the comparator is modelled by applying a HR to the intervention, the choice of waning method has a minimal impact on the results, and only the choice between immediate or gradual waning results in any non-negligible variation.
- The absence of mature data commonly results in uncertainty regarding long-term extrapolation, particularly for novel therapies such as IOs. Consequently, the results of this case study indicate that gradual waning methods based on the equalization of hazards may represent the most appropriate approaches for reducing variation in projected survival outcomes in instances where there is uncertainty associated with the choice of the most appropriate curve for the intervention.
- Given the variation between treatment waning methods, further methodological guidance and transparency in the implementation of waning methods would be valuable for future HTA and cost-effectiveness assessments.

References

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