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**Evidence Review Group Report commissioned by the
NIHR HTA Programme on behalf of NICE**

**Nivolumab for treating relapsed or refractory classical Hodgkin
lymphoma**

ADDENDUM

Additional information requested by the National Institute for Health
and Care Excellence

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Key to colour highlighting used in addendum

Academic in confidence (AIC) information in yellow.

Commercial in confidence (CIC) information in blue.

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1 Introduction

This is an addendum to the Evidence Review Group (ERG) report for the single technology appraisal (STA) “Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma”. At the request of the National Institute for Health and Care Excellence (NICE), the ERG has provided the following additional information to inform the Appraisal Committee Meeting:

- Methods and results of generating a Gompertz overall survival (OS) curve for nivolumab
- Analyses applying the Gompertz OS curve to nivolumab survival in the ERG base case (analysis ERG10 in the ERG report)

2 Generating a Gompertz curve for nivolumab OS

In the company submission, the company fits survival curves to OS using the following curves: exponential, lognormal, log-logistic, Weibull, Gompertz and generalised gamma. In the base case, the Weibull was used to model OS, whilst the exponential, lognormal, and log-logistic curves were explored in sensitivity analyses. As can be seen in Figure 1, the curve with shortest mean survival is the Gompertz curve, predicting mean OS of [REDACTED] months.

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Figure 1 Parameterisation of overall survival (CS Figure 26 , page 106)

There is a great deal of uncertainty in the OS estimates for nivolumab patients in the trial population as the OS data are immature. AiC and BiC data showed that all curves were a reasonable fit for nivolumab survival and therefore the choice of curve has been based on clinical plausibility. In order to further explore the uncertainty around OS, the committee lead team requested that the ERG conduct analyses using the Gompertz curve to estimate overall survival for nivolumab, as a clinician on the lead team believed that mean OS was likely to be shorter than the [REDACTED] years predicted by the Weibull OS model.

$$S(t) = e^{-a(e^{bt}-1)} \quad (\text{Equation 1, Gompertz survival function})$$

In order to replicate the Gompertz OS curve (Equation 1, above) for nivolumab we attempted to build a curve using the rate (*a*) and shape (*b*) statistics reported in Figure 1 (CS Figure 26, p. 106). This curve did not match the Gompertz curve in Figure 1 and the CS did not provide details of the Gompertz survival function used. However, because the Gompertz curve is a two

parameter model and because we know that the mean survival for the curve is 41.7 months, we were able to provide plausible parameters ($a = \blacksquare$, and $b = \blacksquare$) for use with the Gompertz equation above which produced a curve that matched Figure 1. The survival curve for this recreated Gompertz curve is presented in Figure 2, below. This curve is used in this addendum.



Figure 2 Gompertz curve recreated by the ERG

The ERG has reservations about the use of the Gompertz distribution for modelling nivolumab. Figure 3 shows the hazard for nivolumab overall survival over time. The gradual increase in hazard, with greatest risk at four years and hazard declining quickly thereafter, may not be clinically plausible. Additionally comparing the Gompertz curve to SoC survival curves in the CS and ERG base cases shows that the SoC survival curves cross the Gompertz curve of nivolumab (see Figure 4), which appears unlikely to the ERG.



Figure 3 Nivolumab OS hazard over time for Gompertz curve

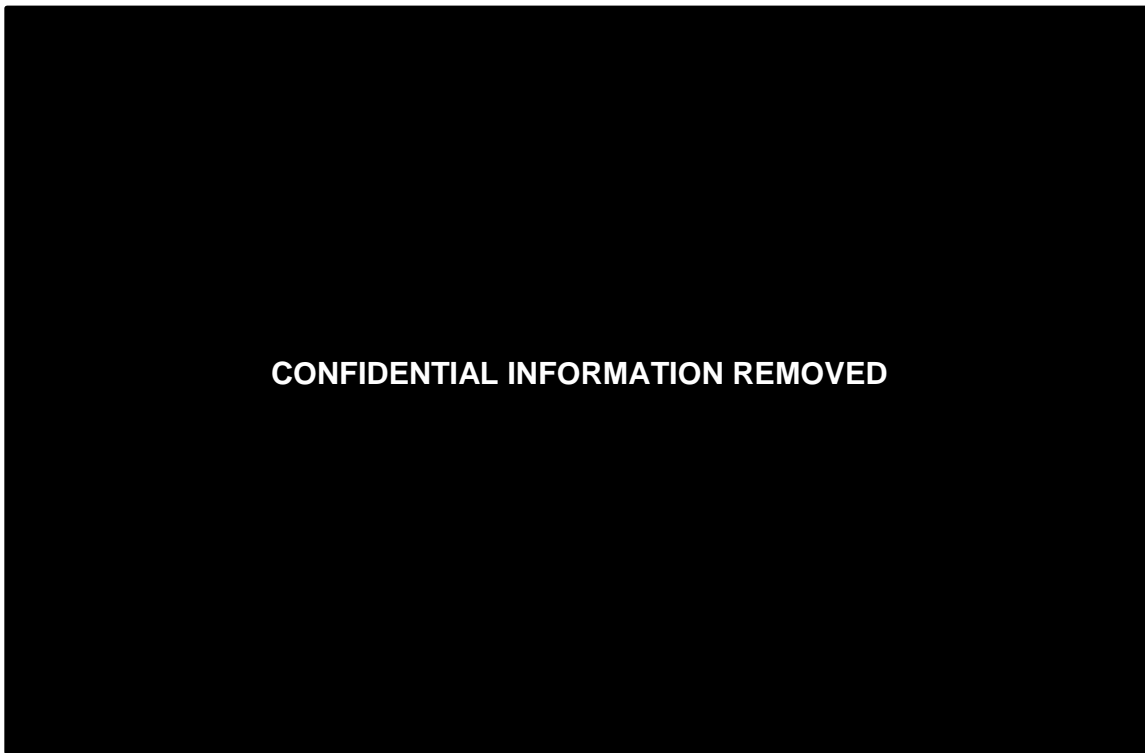


Figure 4 Nivolumab and SoC survival curves

The ERG did not conduct analyses using Gompertz curves for SoC as using the Gompertz curves would have improved survival for SoC. Clinical experts did not find this plausible.

3 Analyses applying the Gompertz OS curve to nivolumab survival in the ERG base case (analysis ERG10 in the ERG report)

The ERG conducted analyses using the ERG Base Case (for assumptions and justifications see Section 4.4 of the ERG report). The ERG ran an analysis replacing all OS curves for nivolumab (pre-progression, post-progression, and alloSCT OS on nivolumab) with the Gompertz survival curve. Table 1 reports the results of this analysis.

Table 1 Results of ERG Addendum analyses containing alloSCT

#	Analysis	Nivolumab		SoC		ICER £/QALY)
		Costs	QALY	Costs	QALY	
ERG10	ERG Base Case ^a	██████	██████	£23,043	2.102	£36,525
ERGADD1	ERG Base Case, Nivolumab OS using Gompertz	██████	██████	£23,043	2.102	£122,825

^a see Table 65, p. 152-153 in ERG report

4 Conclusions

There is substantial uncertainty on the long-term effectiveness of nivolumab and its comparator, SoC. NICE requested that the ERG produce an analysis using the Gompertz curve for overall survival for nivolumab. The ERG have produced this analysis although they have reservations about how clinically plausible the Gompertz curve may be. Unfortunately, the uncertainty around overall survival is unlikely to be resolved without further empirical data.