Addendum: Pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable: A Systematic Review

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1 Revised pembrolizumab discount rate

The company had submitted a discount rate for pembrolizumab which included VAT, when VAT should have been excluded. The company have now (as of 2nd March 2018) revised the discount rate to exclude VAT, lowering it from [redacted] Based upon the ERG's checking of the health economic model, the company have used their original model for incorporating the new discount, rather than the model provided during the clarification process which corrected for a couple of errors within the original model. These errors did not have a substantial impact upon the company's ICERs; however it would have been preferable to incorporate the revised discount within the corrected model submitted during the clarification process. The probabilistic ICERs for pembrolizumab compared with carboplatin plus gemcitabine for the original submission and the clarification letter were £35,211 and £37,081 per QALY gained respectively. The updated company probabilistic ICER incorporating the new discount, using the model from the original submission, is £35,961 per QALY gained.

The ERG has incorporated the revised discount into their base case, leading to a deterministic ICER for pembrolizumab compared with carboplatin plus gemcitabine of £65,642 per QALY gained and a probabilistic ICER of £67,068 per QALY gained, as shown in Tables 1 and 2 below.

Table 1: ERG's deterministic results using discount without VAT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£20,065	1.10	0.70				
Pembrolizumab	£51,868	1.89	1.19	£31,803	0.79	0.48	£65,642
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 2: ERG's probabilistic results using discount without VAT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£20,292	1.13	0.72				
Pembrolizumab	£51,974	1.90	1.19	£31,682	0.77	0.47	£67,068
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

2 Clinical effectiveness results of KEYNOTE-052

The company also submitted new clinical effectiveness results of KEYNOTE-052 based on a more recent data cut-off point 30th Nov 2017. The company reports a [redacted] whereas based on 9th March 2017 cut-off point presented within the CS, the median duration of follow-up for all patients was 9.5 months (range 0.1-22.7 months); mean 9.4 months (SD 5.5 months).

[redacted]

The company states that the updated OS and PFS data have been incorporated into the health economic model, but not the simulated treatment comparison. No details were given in terms of how the updated data were used. Based upon the ERG's checking of the company's health economic model, the company used the same piecewise parametric modelling approach based on the new OS and PFS data. The same data cut-off points for the piecewise analyses (9 weeks for PFS and 32 weeks for OS) and the same curve choice beyond the data cut-off points (Weibull for PFS and log normal for OS) were used as in their original submission. The company obtained a new set of coefficients and variance-covariance matrices for each parametric distribution used to model PFS and OS of patients receiving pembrolizumab. Since the company have not provided a description of their analyses, it is not clear to the ERG the justification of the model choice given the new evidence. As for the analyses using the updated discount for pembrolizumab, the company apply the new estimates for OS and PFS within their original model (which contains errors which were corrected within the clarification process).

The ERG notes that they did not have sufficient time prior to the committee meeting to be able to undertake new analyses based on the new data. Hence, the ERG uses the updated OS and PFS data to validate the ERG's extrapolation model choice in the original ERG report. Table 3 and Table 4 show the comparison of the ERG's model choices, the company's base case model given the two data cut-off points and the observed KM data. Given the updated OS KM data at 22.5 and 28.5 months, the ERG believes that the ERG's original base case model (log normal) remains potentially the most plausible model. This new data also suggests that the generalised gamma, which provides similar extrapolated long-term survival benefit as the company's base case, is unlikely to be plausible.

Given the updated PFS data, the ERG believes that the ERG's original base case model (spline k=3) may have underestimated the PFS benefit, hence the ERG has revised the base case to spline k=2,

taking into account the updated PFS data and the relationship with the extrapolated OS curve.

The ERG also notes that new time on treatment data have not been provided by the company.

Table 3: Extrapolated long-term overall survival probability for pembrolizumab

Time point	Observed Kaplan Meier (9 March 2017)	Observed Kaplan Meier (30 Nov 2017)	ERG's model					Company's base case (Kaplan-Meier data up to 32 weeks and a log normal distribution beyond 32 weeks)	
			Generalised gamma	Log normal (base case)	Spline k=1, scale=hazard	Spline k=2, scale=hazard	Spline k=3, scale=hazard	Using 9 March 2017 data	Using 30 Nov 2017 data
22.5 months	0.37	[redacted]	0.32	0.31	0.32	0.31	0.30	0.32	[redacted]
28.5 months	-	[redacted]	0.27	0.25	0.26	0.25	0.23	0.27	[redacted]
5 years	-	-	0.14	0.11	0.10	0.08	0.07	0.15	[redacted]
10 years	-	-	0.07	0.04	0.02	0.01	0.01	0.07	[redacted]
20 years	-	-	0.03	0.01	0	0	0	0.03	[redacted]

Table 4: Extrapolated long-term progression-free survival probability for pembrolizumab

Time point	Observed Kaplan Meier (9 March 2017)	Observed Kaplan Meier (30 Nov 2017)	ERG's model			Company's base case (Kaplan-Meier data up to 9 weeks and a Weibull distribution beyond 9 weeks)	
			Spline k=1, scale=hazard	Spline k=2, scale=hazard (new base case)	Spline k=3, scale=hazard (original base case)	Using 9 March 2017 data	Using 30 Nov 2017 data
22.5 months	0.16	[redacted]	0.16	0.15	0.13	0.12	[redacted]
28.5 months	-	[redacted]	0.14	0.13	0.09	0.09	[redacted]
5 years	-	-	0.09	0.07	0.03	0.03	[redacted]
10 years	-	-	0.06	0.03	0.01	0.01	[redacted]
20 years	-	-	0.03	0.01	0	0	[redacted]

Tables 5 and 6 show the ERG's deterministic and probabilistic model results with the PFS of pembrolizumab using spline k=2 rather than spline k=3 as well as the revised discount rate for the cost of pembrolizumab. There is a 0% and 9% probability of pembrolizumab being cost-effective at thresholds of £30,000 and £50,000 per QALY gained respectively. Due to the different direction of effect of the two changes, the ERG's ICERs do not alter substantially from their original base case.

Table 5: ERG's deterministic results using discount without VAT and new data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£20,065	1.10	0.70				
Pembrolizumab	£52,184	1.89	1.21	£32,119	0.79	0.50	£63,673
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 6: ERG's probabilistic results using discount without VAT and new data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin+ Gemcitabine	£20,292	1.13	0.72				
Pembrolizumab	£52,261	1.90	1.21	£31,969	0.77	0.49	£65,252
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

3 Sensitivity analyses

Given that the parameters varied by the company in their univariate sensitivity analyses do not impact upon the ERG model results substantially, the ERG has not rerun those analyses. The ERG has, however rerun their additional sensitivity analyses (described in Section 5.3.2 of the ERG report) using the pembrolizumab discount without VAT and the revised PFS curve choice. The ERG did not rerun the analysis using the generalised gamma for OS given that it was no longer thought to be plausible by the ERG given the new data. The results of these analyses are presented in Table 7. As before, these analyses show that the ICER is highly uncertain.

Table 7: Scenario analysis undertaken by the ERG

Parameter modified	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic base case	£32,119	0.79	0.50	£63,673
Alternative distributions for pembrolizumab OS (base case = lognormal)(£/LY)				
Spline k=1, scale=hazard	£31,544	0.71	0.46	£68,782
Spline k=2, scale=hazard	£30,443	0.56	0.37	£83,306
Spline k=3, scale=hazard	£29,763	0.47	0.31	£96,645
Alternative assumptions about pembrolizumab stopping rule/ efficacy following treatment discontinuation				
Assume no stopping rule; treatment continues based on the ToT/ OS curve treatment continues based on the PFS curve	£68,838 £58,469	0.80 0.80	0.51 0.51	£134,978 £114,647
Assume that HR=1 for PFS and OS at 3 years	£32,142	0.79	0.51	£63,481
2 year time horizon	£26,222	0.15	0.10	£261,898
Utility value in the progressed state for both treatment groups				
Reducing the utility from 0.61 to 0.55	£32,119	0.79	0.49	£66,016
Monitoring costs				
Half the cost of monitoring	£29,064	0.79	0.50	£57,616
Cost of carboplatin				
Half the cost of carboplatin	£32,205	0.79	0.50	£63,842