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

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1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) adequately describes the decision problem. The CS assesses the clinical and cost-effectiveness of pembrolizumab (Keytruda®), within its licensed indication for the treatment of adults patients with locally advanced or metastatic urothelial carcinoma who have not received prior systematic chemotherapy and who are not eligible to receive cisplatin.

The comparators considered in the CS differ from the National Institute for Health and Care Excellence (NICE) final scope: only carboplatin plus gemcitabine was included as a comparator but atezolizumab and best supportive care (BSC) were excluded. The Evidence Review Group (ERG) agrees that the evidence for atezolizumab was too uncertain to enable a useful comparison. The ERG also agrees that BSC should be excluded due to a paucity of evidence. The ERG's clinical advisors suggest that gemcitabine plus carboplatin has been used for many years in this population, despite being unlicensed for this indication, hence no trials have been undertaken to compare the combination with BSC.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included a systematic review of the clinical effectiveness evidence. The KEYNOTE-052 study provides the main supporting clinical effectiveness evidence for this submission and is a Phase II, single-arm, open-label, non-randomised study. KEYNOTE-052 was designed to test the efficacy and safety of pembrolizumab in patients with advanced/unresectable or metastatic urothelial cancer where cisplatin is unsuitable. It is important to note that the KEYNOTE-052 study is ongoing. Different data cut-off points are used in the CS and clinical study report (CSR) (both 9th March 2017), and Balar *et al*. (2017) and the European Public Assessment Report (EPAR) (both 1st Sept 2016).

The CS states that KEYNOTE-052 was conducted in 16 countries. In KEYNOTE-052, 370 patients received at least one dose of pembrolizumab. The study population was predominantly male (77.3%) and white (88.6%) with 78.1% of the patients having an ECOG status of 1 (36.2%) or 2 (41.9%). The median age of study participants was 74 years (range 34-94 years). With regard to metastases location, 51 patients (13.8%) had lymph node only, while 315 patients (85.1%) had visceral disease and four patients (1.1%) had metastases location not reported. Pembrolizumab was administered in an un-blinded manner at a dosage of 200mg via intravenous (IV) infusion over 30 minutes every 3 weeks. Pembrolizumab treatment could continue for 24 months.

year (QALY) gained for pembrolizumab compared with carboplatin plus gemcitabine, based upon the results within their health economic model.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The systematic review presented in the CS appears to be comprehensive. The health economic model submitted by the company was generally well described and justified.

1.6.2 Weaknesses and areas of uncertainty

The uncertainties in the clinical evidence are mainly concerned with the absence of any RCTs comparing pembrolizumab with carboplatin plus gemcitabine, atezolizumab or BSC. The only comparator included in the CS is carboplatin plus gemcitabine. In addition, the data from KEYNOTE-052, reported in the CS are immature. The estimated completion date of the study is 21st June 2018 according to Clinical trials.gov (https://clinicaltrials.gov/ct2/show/NCT02335424).

Due to the lack of head-to-head studies, the relative treatment effect of pembrolizumab is uncertain. The ERG believes that the company's simulated ITC lacks validity, and because of this the benefits of pembrolizumab are likely to be overestimated within the company's health economic model. There is also substantial uncertainty around the extrapolation of the survival curves. In addition, it is unclear whether a treatment stopping rule would be applied in practice, and if so it is unknown what impact this would have upon treatment effectiveness. These structural uncertainties were insufficiently explored by the company within their scenario analyses, and hence the full range of plausible ICERs given the available evidence was not presented by the company.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has corrected errors relating to the implementation of utilities and to the proportion of males for the calculation of other-cause mortality. The ERG has also employed an approach where utilities are varied according to progression status rather than time until death. In addition, the ERG has included extrapolation of the unadjusted trial data for pembrolizumab from KEYNOTE-052 and carboplatin plus gemcitabine from De Santis (2012) as part of their base case, as well as incorporating a hazard ratio of 1.0 for PFS and OS for pembrolizumab versus carboplatin plus gemcitabine after 24 months of treatment given the proposed stopping rule. The ERG's changes to the utility approach and the extrapolation of survival data have a substantial impact upon the ICER.

The ERGs probabilistic base case ICER is £66,588 per QALY gained. The scenario analyses run by the ERG suggest that the ICER is highly uncertain. In particular, the choices of extrapolation for the OS of pembrolizumab and the stopping rule for pembrolizumab have the largest impacts upon the

4.4.3 Model selection in STC

The company conducted a non-standard STC by incorporating bootstrapping to produce estimates of variability. The company claims that the bootstrapping procedure maximises the full use of the IPD. A bootstrap sample is a random sample with replacement generated from the original IPD in KEYNOTE-052 study. The company states that on average about 1/3 of the patients were not included in each bootstrap sample and called these patients out-of-bag (OOB).

The Cox proportional hazards model was used to develop the regression model. Four competing models were fitted to bootstrap samples, where one model had the full set of covariates containing ECOG ≥2, renal failure, presence of liver metastases or visceral metastases, and primary tumour site (upper or lower). Three other models had the full set of covariates plus one interaction variable comprised of ECOG performance status and either liver metastasis, visceral metastasis or renal function.

Model selection was based on the OOB predictive performance. The company defined the sum of Akaike Information Criterions (AICs) to be the sum of the differences between the observed KM survival estimates minus the predicted OOB survival estimates at every failure time in the original IPD KM curve. The model with the lowest sum of AICs would be chosen as the final model. If all models provide similar AICs, then the simplest model would be chosen. The best regression model for both PFS and OS was the simplest model with the full set of four prognostic factors, i.e., ECOG ≥2, liver metastasis, poor renal function, visceral metastasis and upper urinary tract. The estimated coefficients can be found in the CS Table 25 and 32.

The ERG notes that the company's definition of AIC is not a standard one used in model selection in general.

4.4.4 Prediction of outcomes in STC

The company simulated a large number of hypothetical individuals based on the reported marginal distribution of the covariates of interest and the correlation from KEYNOTE-052 study. When a covariate value was missing, a random sample from a uniform distribution with boundaries defined by the range of reported values across the included studies. The company also generated the predicted log-hazards. The mean of the predicted log-hazard and the variance of the log-hazard from bootstrap samples were used in the fractional polynomial models in obtaining the estimate for the indirect comparisons.

Intervention

The intervention under consideration within the company's health economic analysis is pembrolizumab. Pembrolizumab is assumed to be administered by IV infusion over thirty minutes at a fixed dose of 200mg every three weeks. Treatment is continued until progression occurs, unacceptable toxicity occurs or the patient or their representative withdraws consent. The company suggests that patients will stop pembrolizumab after a maximum of 24 months of treatment, as per the KEYNOTE-052 protocol. The SmPC does not limit treatment to 24 months, stating that 'Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.' In some cases patients are allowed to continue treatment beyond progression if some clinical benefit is still being obtained from the treatment.

Comparators

The comparators specified in the NICE final scope were carboplatin plus gemcitabine, atezolizumab and BSC. The CS only compares pembrolizumab with carboplatin plus gemcitabine. The company states that atezolizumab appears to be an effective first line treatment option for cisplatin ineligible patients with locally advanced or metastatic urothelial carcinoma. However, they also state that it has been difficult for the NICE committee to establish the size of the clinical benefit achievable and thus the drug has been made available through the Cancer Drugs Fund, and as such, they argue that atezolizumab is not a relevant comparator. Given that the Final Appraisal Determination issued by NICE suggested that the benefits of atezolizumab were too uncertain to recommend outside of the CDF currently, and given that the studies of atezolizumab and pembrolizumab both adopt a single-arm design, the ERG agrees that a comparison with atezolizumab would not be helpful for informing the current decision.

BSC has also not been considered a relevant comparator due to a paucity of evidence. Within their submission, the company suggests that most patients would receive carboplatin plus gemcitabine rather than BSC, although in clarifying why KEYNOTE-052 was not designed as a randomised trial (clarification response,question A9), the company state that 'the most appropriate randomised clinical trial in this setting would be to compare pembrolizumab to BSC as control'. The clinical advisors to the ERG suggested that most patients would receive gemcitabine plus carboplatin. The ERG has searched for clinical evidence for the use of BSC compared with any other treatment for this population (see Section 4.1), although none was identified. The ERG's clinical advisors also suggested that carboplatin plus gemcitabine has been used for many years in this population, despite being unlicensed for this indication, hence no trials have been undertaken to compare the combination with BSC. As such, given current evidence, it is not possible for the company to provide a comparison with BSC.

Figure 9) suggested that neither the Weibull nor the exponential were an appropriate choice. The ERG believes that a piecewise analysis is not necessary for OS, but may have some merit for PFS as a single standard parametric distribution may not be flexible enough to model the PFS.

The ERG questioned the validity of the extrapolated curves for carboplatin plus gemcitabine arm in clarification question B7, as the median PFS and OS predicted by the model for carboplatin plus gemcitabine were 2.53 months and 7.36 months, respectively. These appear to be underestimated compared with the median PFS and OS reported in the published papers[16-19] (between 4.4-5.8 months and 7.2-10 months, respectively). In the company's response, they explained that this is due to the population adjustment to balance the cross-study differences. As discussed in Section 4.4.4, there was no clear indication that the patients in KEYNOTE-052 were less fit or frailer than the patients in the carboplatin plus gemcitabine studies. Hence, the ERG suggests that the average of 2 months short in both PFS and OS seems to be implausible.

5.2.7 Adverse events

Within the model, any Grade ≥3 AEs that occurred in at least five percent of patients in either treatment arm is included. In addition, the proportion of patients experiencing diarrhoea is included from Grade ≥2 and the proportion of patients experiencing febrile neutropenia is included at any grade. All AEs are assumed to occur in the first treatment cycle.

Evidence around the incidence of AEs for patients receiving pembrolizumab was taken from data collected within the KEYNOTE-052 study and presented in the CS (page 266). Incidence of AEs in patients receiving the comparator treatment was obtained from a weighted average of the studies included in the NMA for efficacy. The percentage of patients receiving pembrolizumab and carboplatin plus gemcitabine experiencing each AE is presented in Table 23. Those AEs that occurred in less than 5% of patients were not included for that treatment group.

Table 1: Percentage of patients experiencing each included adverse event

Adverse Event	Pembrolizumab	Carboplatin plus gemcitabine
Anaemia	7.57%	7.14%
Diarrhoea	5.41%	0.45%
Fatigue	5.14%	<5%
Febrile neutropenia	<5%	4.46%
Infection	<5%	6.25%
Leukopenia	<5%	23.66%
Neutropenia	<5%	34.38%
Thrombocytopenia	<5%	30.80%
Urinary tract infection	10.54%	<5%

Utilities and costs associated with these adverse events are described in Sections 5.2.8 and 5.2.9.

5.2.8 Health-related quality of life

The company conducted a search of published literature to identify relevant HRQoL studies for use in the model.

Search strategies

The searches for published evidence on HRQoL were conducted at the same time as the cost-effectiveness review (August 2015, updated August 2017). The search strategies are reported in full in the CS Appendix G.1. The same range of databases was used, however this time no date limits were applied and the economic filter was replaced by a different set of terms. Again, no acknowledgement is made of the source of these terms; although the ERG considers them to be broadly fit for purpose, it is not possible to confirm whether their sensitivity and specificity have been validated.

Study selection

A total of 24 studies were included. Of these, 5 studies reported HRQoL data collected in a first line treatment setting and sixteen studies reported HRQoL data collected in a second line or subsequent treatment setting. The setting in the three remaining studies was unclear.

The company states that the HRQoL evidence in these studies was limited, with the most relevant evidence coming from the NICE TA of Atezololizumab in urothelial cancer, which was based on an appraisal of vinflunine for urothelial cancer patients who have received prior therapy carried out by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and derived through mapping. However, as these patients had received prior treatment, the company states that they are unrepresentative of the patient population relevant to this appraisal. Thus, the company uses utility data obtained during the KEYNOTE-052 study and presented in the CS (pages 95-98).

Utilities used in the model

During the KEYNOTE-052 study, the company collected HRQoL data using the EQ-5D questionnaire during treatment cycles one, two, three, four and every two cycles thereafter up to a limit of one year or the end of treatment, whichever happened first. HRQoL was also measured at 30 days post treatment discontinuation. However, they estimated utility values in two different ways: (i) based on patients' disease state, so that patients had a different utility in the progression-free health state and the progressed disease health state; and (ii) based on patients' time to death, with this being divided into five categories:

1. Time to death greater than or equal to 360 days
2. Time to death greater than 180 days but less than or equal to 360 days
3. Time to death greater than 90 days but less than or equal to 180 days
4. Time to death greater than 30 days but less than or equal to 90 days
5. Time to death less than 30 days.

It should be noted that for a time to death of less than 360 days, only patients with an observed time to death were included whilst censored patients were excluded. For patients whose time to death was at least 360 days, censored patients were included only if their censored time to death was at least 360 days.

Linear mixed effects models with random intercept were used by the company to estimate utilities in order to include the correlation of repeated measures for individual patients. AEs were included as a covariate within this analysis to provide an estimate for the disutility associated with experiencing an AE (see below for more details).

The company used the time to death approach in their base case, arguing that there is a gradual decrease in HRQoL as patients get closer to death, which might not be captured with a simple measurement post-progression in the progression-based utilities.l. They also highlight that it has been used in other NICE submissions to estimate HRQoL in patients with urothelial carcinoma[6] and advanced melanoma.[32-34] The utilities obtained using both approaches are presented in Table 24. Within the model, these utilities were age-adjusted, based on a study by Ara and Brazier[35], although the ERG found that this had been implemented incorrectly (see below).

Whilst the KEYNOTE-052 protocol states that patients will stop pembrolizumab treatment after 24 months, at the March 2017 data cut-off no patients had been treated with pembrolizumab for 24 months; hence there is no evidence around the impact of this stopping rule upon the effectiveness of pembrolizumab beyond treatment discontinuation. The company's model assumes that the effectiveness estimates of patients whilst on treatment can be extrapolated to represent patients who are no longer receiving treatment. The clinical advisors to the ERG suggested that patients who have received pembrolizumab may maintain some benefit following discontinuation and there is some evidence in patients with advanced melanoma that pembrolizumab may provide benefit beyond treatment discontinuation where a stopping rule is implemented.[36] However, the ERG suggests that it is unlikely that patients can discontinue pembrolizumab treatment after 2 years and yet continue to achieve benefits from that treatment for a further 18 years. A RCT by Spigel compared one year of nivolumab treatment with continuous nivolumab treatment in patients with non-small cell lung cancer, which found that PFS was significantly better in those that had continued treatment.[37]

During the clarification process, the ERG asked the company to consider alternative assumptions around the long-term efficacy of pembrolizumab given the stopping rule. The company stated that they had incorporated the functionality to set the hazard ratio to 1 at 3, 5 and 10 years within the model, but they incorrectly adjusted the survival curves of the comparator rather than those of pembrolizumab. The ERG has therefore revised this analysis within their base case model, adjusting the pembrolizumab survival curves rather than the carboplatin plus gemcitabine curves (see Section 6.1).

Drug acquisition costs

Acquisition costs for pembrolizumab were taken from the CS. The recommended optimum dose of pembrolizumab is 200mg on day 1 of each 21-day treatment cycle whilst a patient is progression-free. The list price of pembrolizumab is £5,260 for two 100mg vials, [redacted]. All of the company's analyses (and subsequent ERG analyses) use the price of pembrolizumab [redacted].

Acquisition costs for the comparator drugs were taken from the Electronic Market Information Tool (eMIT) in June 2017.[38] As carboplatin in combination with gemcitabine is not licensed for urothelial carcinoma, the company took the dose information from the protocol for the KEYNOTE-361 trial.[39] Carboplatin is assumed to be administered at a dose of 400mg/m^2 on day 1 of each 21-day treatment cycle and gemcitabine at a dose of 1000mg/m^2 on days 1 and 8 of each 21-day treatment cycle. Assuming a mean patient body surface area of 1.88m^2 from the KEYNOTE-052 study[11] and vial

- Assuming pembrolizumab and combination gemcitabine and carboplatin treatment are equivalent in terms of PFS, based on the PFS observed in the KEYNOTE-045trial;
- Using a fully fitted parametric curve for overall survival of patients receiving pembrolizumab;
- Using a 44 weeks cut-off for the piecewise approach for the overall survival of patients receiving pembrolizumab;
- Using a 15 weeks cut-off for the piecewise approach based on the second tumour assessment for the overall survival for patients receiving pembrolizumab;
- Using utility values based on disease state rather than time to death;
- Removing age-related utilities from the model.

Within the clarification process, the company also provided scenario analyses using alternative parametric curves for the OS extrapolation of pembrolizumab, alternative assumptions about the pembrolizumab stopping rule and inclusion of grade 3 or greater AEs of Special Interest occurring in >1% of pembrolizumab patients.

Subgroup analyses

In addition, the company considered subgroups according to PD-L1 status, of CPS≥1% and CPS≥10%. This analysis assumed that an additional cost associated with PD-L1 testing would be required, as shown in Table 30.

Table 2: Cost of PD-L1 testing per patient eligible for pembrolizumab who express PD-L1 status (reproduced from Table 64, page 119 CS)

Description	CPS≥1%	CPS≥10%
PD-L1 test cost	£40.50	£40.50
Percentage of patients eligible for treatment with pembrolizumab who express PD-L1 status among newly diagnosed patients with stage 4 urothelial cancer	37.2%	14.5%
Total PD-L1 costs	£108.88	£279.08

The company state that they conducted the subgroup analysis because it was pre-specified in the NICE final scope; however they highlight that this analysis is based on a small number of patients and therefore the results should be interpreted with caution. The ERG notes that there is no evidence by subgroup for the comparator; hence it was not appropriate to conduct the ITC for the subgroups.

5.2.11 Cost-effectiveness results

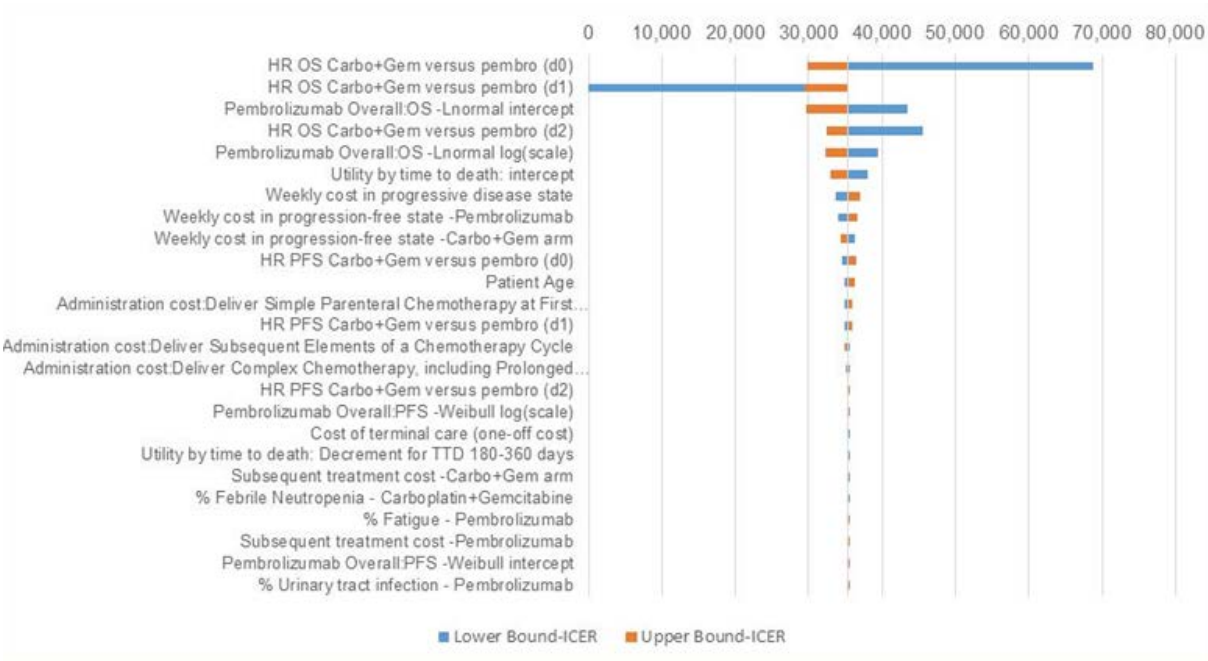
Base case results

The company's base case deterministic cost-effectiveness results, as presented in the company's clarification response, including the [redacted]

Univariate sensitivity and scenario analyses

The company presented the results of their univariate sensitivity analyses within a tornado diagram. Within the clarification response (Appendix 1) this was based upon net monetary benefit (NMB) rather than on an ICER. This assumed a willingness to pay threshold of £50,000 per QALY gained. The health economic model, however, also included a tornado plot based on the ICER, presented in Figure 13 below.

Figure 1: The company's tornado diagram using NMB (reproduced from 'OWSA' sheet of health economic model provided in clarification response)



The company also undertook some scenario analyses, as shown within Table 33. These analyses suggest that, of those assumptions tested, the choice of method for estimating HRQoL over time and the extrapolation of OS have the greatest impact upon the model results. The ICER for pembrolizumab compared to carboplatin plus gemcitabine remains between £30,000 and £43,000 per QALY gained for all analyses tested. However, the ERG suggests that not all plausible alternative assumptions have been tested within the scenario analyses. Whilst the company have tested 'PFS equivalence between arms' this does not alter the OS, and given that PFS is only used as a proxy for time on treatment with carboplatin and gemcitabine and to estimate costs incurred whilst in the progressed disease state in the company's base case, it has a very small impact upon the ICER, as would be expected.

As part of their clarification response, the company tested the impact upon the model results using alternative parametric distributions for extrapolating OS and PFS (see clarification question B6). The model results did not change substantially when the distribution for extrapolating PFS was altered; this is unsurprising given that within the company's base case model, PFS is used only as a proxy for time on treatment for carboplatin plus gemcitabine and to estimate costs incurred whilst in the progressed disease state. However, this analysis shows that the results of the model are highly dependent upon the choice of extrapolation approach for the OS associated with pembrolizumab (see Table 34), and all of these scenarios use the KM data until 32 weeks and then only amend the extrapolation approach beyond this time point.

Table 3: Company results using alternative parametric distributions for pembrolizumab overall survival (reproduced from Table 17, clarification response B6)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Log-normal – Base case						
Carboplatin+ Gemcitabine	£18,011	0.86	0.55	-	-	-
Pembrolizumab	£53,645	2.25	1.55	£35,634	1.01	£35,341
Exponential						
Carboplatin+ Gemcitabine	£17,572	0.79	0.50	-	-	-
Pembrolizumab	£48,157	1.44	0.97	£30,586	0.47	£64,407
Weibull						
Carboplatin+ Gemcitabine	£17,525	0.79	0.49	-	-	-
Pembrolizumab	£47,865	1.40	0.94	£30,340	0.45	£67,585
Gompertz						
Carboplatin+ Gemcitabine	£18,803	0.97	0.63	-	-	-
Pembrolizumab	£58,689	3.00	2.09	£39,886	1.46	£27,411
Log-logistic						
Carboplatin+ Gemcitabine	£17,736	0.82	0.52	-	-	-
Pembrolizumab	£51,828	1.98	1.36	£34,092	0.85	£40,339
Generalised gamma						
Carboplatin+ Gemcitabine	£18,069	0.87	0.55	-	-	-
Pembrolizumab	£54,237	2.34	1.62	£36,168	1.06	£33,977

As part of the clarification process, the company also tested the impact of excluding the treatment stopping rule for pembrolizumab (clarification question B9). The company showed that in the absence of a 24-month stopping rule, the ICER for pembrolizumab compared with carboplatin plus gemcitabine would increase to £85,084 per QALY gained (see Table 35). Time on treatment is

assumed to follow the Gompertz distribution within this anlaysis, as in the company's base case. Since the Gompertz curve plateaus out, time on treatment may be overestimated in this analysis and hence the cost of pembrolizumab may also be overestimated.

Table 4: Company results using no stopping rule for pembrolizumab (reproduced from Table 20, clarification response B9)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Carboplatin+ Gemcitabine	£18,011	0.86	0.55	-	-	-
Pembrolizumab	£103,802	2.25	1.55	£85,791	1.01	£85,084

During the clarification process, the company also tested having a reduced pembrolizumab treatment effect at 3, 5 and 10 years by setting the hazard ratio between pembrolizumab and carboplatin plus gemcitabine for OS and PFS to 1.0 following treatment discontinuation at 2 years (clarification question B9). However, the company implemented this analysis by altering the PFS and OS estimates of carboplatin plus gemcitabine rather than those of pembrolizumab within this analysis. The analysis suggested that this would have a minimal impact upon the model results.

During the clarification process, the company also tested the impact of incorporating any grade 3 or greater AEs of Special Interest occurring in ≥1 of patients in the pembrolizumab group (clarification question B11). This showed that the cost of AEs does not have a substantial impact upon the model results.

Subgroup analysis results

The results of the company's subgroup analyses are presented in Table 36 and Table 37. These suggest that a patients' PD-L1 status appears to have only a minor impact upon cost-effectiveness. However, the company appropriately warns that these results should be treated with caution because they are based on small numbers. The ERG does not undertake any additional analyses on these subgroups given that there is no evidence on these subgroup populations for the comparator.

3) Extrapolation of OS and PFS using unadjusted data

The ERG has concerns about the validity of the STC undertaken by the company (see Section 4.4). Given that we do not have the IPD to undertake our own population adjustment analyses, the ERG used a naïve indirect comparison based on the carboplatin plus gemcitabine arm from De Santis (2012)[16] and KEYNOTE-052. The reason to only include De Santis (2012)[16] is because the ERG believes that it may not be appropriate to synthesise the evidence from the four carboplatin plus gemcitabine studies due to the heterogeneity with regard to patients and dosage and administration of gemcitabine and carboplatin (see Section 4.3); and De Santis (2012)[16] is the largest and most rigorously conducted studies in the population of interest. The ERG notes that the naïve indirect comparison doesn't adjust for bias due to cross-study differences. The bias due to imbalance in the observables may be minimal in this case because De Santis (2012)16 and KEYNOTE-052 have similar patient baseline characteristic distributions. The results of the naïve indirect comparison should be interpreted with caution as it does not account for residual bias.

The ERG reconstructed IPD from the observed pembrolizumab data in KEYNOTE-052 for both OS and PFS using the algorithm proposed by Guyot *et al* (2012)[25] and extrapolated the survival benefit using standard parametric distributions including exponential, Weibull, log logistic, log normal, Gompertz, gamma and Generalised gamma and natural cubic spline models by Royston and Parmar[49] with knots={1, 2, 3} based on modelling the log of the cumulative hazard function. When reconstructing the IPD, the ERG used the reported KM data in the economic model directly instead of digitising the KM curves.

Spline based survival modelling approach models the logarithm of the baseline cumulative hazard function or odds function as a natural cubic spline function of log time. This is a more flexible approach compared with using standard parametric distribution. Spline base approach is able to model more complex hazard functions. Natural cubic spline functions are piecewise cubic polynomials defined to be continuous at knots, and linear beyond boundary knots. The complexity of the model is governed by the number of knots. When there is no internal knot, the cubic spline model reduces to either Weibull, log-logistic or log normal distribution. Royston and Parmar[49] suggested to use maximum 3 internal knots since the fitted curves with more than 3 internal knots are expected to be potentially unstable. They also suggest that the position of the knots does not appear to be critical for a good fit and proposed to use centile-based positions as default.

When compared with the hybrid KM approach as the company performed, the natural cubic spline models have a few advantages: (1) the cubic spline model provides a coherent fit to all the observed data; whereas the cut-off point in the hybrid KM approach is arbitrary and only uses the data beyond

Figure 2: Company and ERG predicted base case overall survival

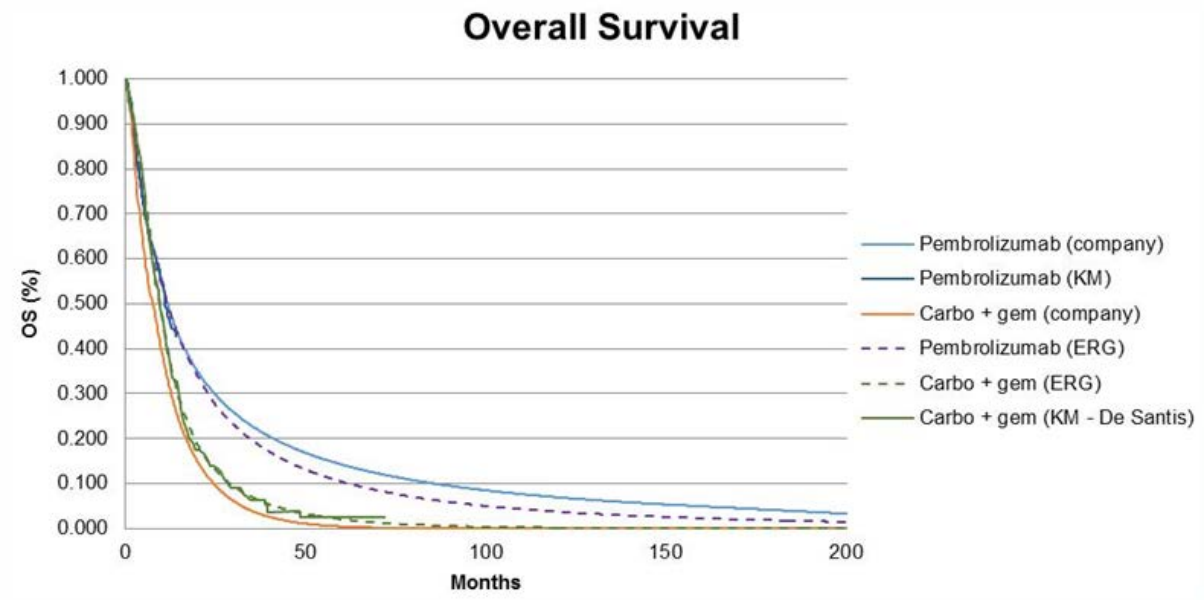


Figure 3: Company and ERG predicted base case progression-free survival

[redacted]

Note: The company's extrapolation of carbo+gem is based on a STC of data from Bamias 2007, Carles 2000, De Santis 2012 and Linardou 2004. The ERG's extrapolation of carbo+gem is based on data from De Santis 2012. All pembrolizumab extrapolation is based upon KEYNOTE-052.

approach whereby utilities are varied according to progression status rather than time until death. In addition, the ERG analyses include the extrapolation of the unadjusted data for pembrolizumab from KEYNOTE-052 and carboplatin plus gemcitabine from De Santis (2012) as part of their base case, as well as incorporating a hazard ratio of 1 for the PFS and OS of pembrolizumab versus carboplatin plus gemcitabine after 24 months of treatment given the proposed stopping rule.

8 OVERALL CONCLUSIONS

The systematic review presented in the CS appears to be comprehensive. The review included is a phase II, single-arm, open-label, non-randomised study (KEYNOTE-052) for pembrolizumab, one RCT (De Santis (2012)[16]; only the carboplatin plus gemcitabine arm is included) and three cohort studies (Bamias (2007)[19], Carles (2000)[17], Linardou (2004)[18]) for carboplatin plus gemcitabine. There was considerable heterogeneity among the comparator studies with regard to patients and dosage and administration of gemcitabine and carboplatin. There was no evidence to suggest that patients in KEYNOTE-052 are less fit or frailer than patients in the comparator studies.

The STC performed by the company to adjust for cross-study differences in patient's baseline characteristics lacks validity as the treatment effect of pembrolizumab for both PFS and OS was more favourable using the adjusted data compared to the observed data in KEYNOTE-052. The ERG does not believe this to be valid because there is no evidence to indicate that the patients in KEYNOTE-052 were less fit or frailer than patients in the comparator studies. For the evidence synthesis, a second fractional polynomial model with p1=p2=0, which estimates time-varying hazard ratios, was chosen as the best fitting model. It was determined in response to clarification that p1=p2=-2 was the overall best fitting model, which provided less favourable results for pembrolizumab when compared with the fractional polynomial model with p1=p2=0. However, only the estimates from the fractional polynomial with p1=p2=0 were used in the economic model.

The company's health economic model is generally appropriate for the decision problem defined in the NICE final scope, though it should be noted that the only comparator tested within the economic evaluation was carboplatin plus gemcitabine. This is because there was no evidence for BSC and the evidence for atezolizumab was too uncertain to enable a useful comparison. The model was generally well described within the CS. The model structure was considered by the ERG to be reasonable; however, as discussed above, the simulated ITC lacks validity and there is substantial uncertainty around extrapolation of the survival curves, which was not explored sufficiently by the company. The company's probabilistic ICER following the clarification process is £37,081 per QALY gained for pembrolizumab compared with carboplatin plus gemcitabine, taken from their health economic model.

The ERG has corrected errors relating to the implementation of utilities and to the proportion of males for the calculation of other-cause mortality. The ERG has also employed an approach where utilities are varied according to progression status rather than time until death. In addition, the ERG has included extrapolation of the unadjusted data for pembrolizumab from KEYNOTE-052 and carboplatin plus gemcitabine from De Santis (2012) as part of their base case, as well as incorporating

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