ID1349 CDF review of TA447

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (CDF review of TA447) ID1349

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (CDF review of TA447)

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Sophie Beale	Critical appraisal of the clinical and economic evidence
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All authors read and commented on draft versions of the ERG report.

1 OVERVIEW

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE). This appraisal is a review of a previous Single Technology Appraisal (STA) of the use of pembrolizumab (Keytruda®) for the treatment of untreated programmed death-ligand 1 (PD-L1) positive (≥50%) metastatic non-small cell lung cancer (NSCLC). Clinical and economic evidence was originally submitted to NICE by Merck Sharp & Dohme (MSD) in October 2016.[1] In June 2017, NICE recommended pembrolizumab (TA447) for use within the Cancer Drugs Fund (CDF) as an option for the treatment of untreated PD-L1 positive metastatic NSCLC in adults, only if:

1. patients' tumours express PD-L1 ≥50% tumour proportion score (TPS) and have no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations
2. pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
3. the conditions in the managed access agreement for pembrolizumab are followed.[2]

The company's main source of evidence for TA447 was the KEYNOTE-024 trial.[3] The original company submission (CS1)[4] provided results from an interim analysis (IA2) of trial data (9 May 2016 cut-off date). The current company submission (CS2)[5] includes data from the final analysis (10 July 2017) and cost effectiveness results that have been generated using the final dataset from the KEYNOTE-024 trial.

Although the quantity of evidence provided by the company was equivalent to that for a STA, the time period for the ERG critique was half of that for a STA. Therefore, as suggested by NICE (emailed letter dated 20 December 2017), the focus of this ERG report is on the company's economic evidence. The ERG has also provided summaries of key clinical effectiveness results alongside those from the analysis of IA2 data presented in CS1.

2 CONTEXT

2.1 Summary of ERG review of original company submission for TA447

The issues relating to KEYNOTE-024 trial design and statistical methods that were highlighted by the ERG in their original (TA447) report[6] are still relevant and are summarised here.

Direct evidence

The company's main source of effectiveness evidence was the KEYNOTE-024 trial. Patients recruited to this trial were randomised to receive either pembrolizumab or standard of care (SOC). The SOC regimens used during the trial included gemcitabine, paclitaxel or pemetrexed with a platinum therapy (cisplatin or carboplatin).

The ERG considers that the KEYNOTE-024 trial was a small, well-conducted, open-label, phase III, randomised controlled trial (RCT). However:

- clinical results from the KEYNOTE-024 trial were only presented for the comparison of treatment with pembrolizumab versus SOC
- the only direct clinical evidence for the comparison of treatment with pembrolizumab versus platinum+pemetrexed came from a subgroup analysis
- the company did not discuss the clinical effectiveness of pembrolizumab compared with single agent chemotherapy
- there was no direct evidence of the clinical effectiveness to allow a comparison of pembrolizumab with the individual comparators listed in the final scope issued by NICE[7]
- the ERG is uncertain of the reasons for, or the implications of, the 3.1 months difference between the blinded independent central review (BICR) assessed progression-free survival (PFS) and the investigator-assessed PFS for patients in the pembrolizumab arm of the KEYNOTE-024 trial (10.3 months versus 7.2 months)
- testing for PD-L1 expression was not routinely available in NHS treatment centres.

Indirect evidence

The company carried out network meta-analyses (NMAs) to generate clinical effectiveness results for comparisons of treatment with pembrolizumab versus all platinum doublet chemotherapies specified in the final scope issued by NICE. Although the ERG considered that the methodology used to conduct the main NMA (all-comers) was appropriate, the ERG considered that the results were unreliable for the following reasons:

- there was extensive heterogeneity between included studies (e.g., PD-L1 status, disease stage, race/ethnicity)
- the unadjusted and adjusted (for treatment crossover) NMA results were very similar
- repeated use of the pembrolizumab data from the KEYNOTE-024 trial may have led to over-inflation of the results due to the possible double-counting of patients in the analyses.

Cost effectiveness evidence

The ERG considered that there were four fundamental issues that cast substantial doubt on the reliability of the company's base case cost effectiveness results for the comparison of treatment with pembrolizumab versus SOC. Three of these issues are still relevant, namely:

1. any extrapolation of overall survival (OS) data from patients in the pembrolizumab arm of the KEYNOTE-024 trial was highly uncertain due to only 35.4% of the total events having occurred
2. the company calculated the cost of pembrolizumab on the basis that treatment would cease after 2 years (35 cycles) as this is in line with details published in the KEYNOTE-024 trial protocol. However, the Summary of Product Characteristics[8] does not include this time dependent stopping rule and the ERG considered it implausible that, in NHS clinical practice, treatment would be stopped at this time point if a patient were deemed to still be deriving clinical benefit from treatment with pembrolizumab
3. the ERG considered that the utility values incorporated into the company model, which were derived from data collected as part of the KEYNOTE-024 trial, were implausibly high, notably for the 360-day period before death when these values were higher than the UK population norms.

2.2 Recent developments

2.2.1 Treatment pathway

Since CS1 (October 2016), as a result of recommendations made by NICE,[9-11] pembrolizumab and nivolumab have become NHS treatment options, after chemotherapy, for many patients with locally advanced or metastatic NSCLC (see Table 1). The company states that PD-L1 targeting therapies are rapidly becoming standard of care for patients who have received prior chemotherapy. The ERG agrees with this statement.

Table 1 Relevant recommendations made by NICE

Identifier	Date	Product	Recommendation
TA428[9]	January 2017 (updated September 2017)	Pembrolizumab	As an option for treating locally advanced or metastatic **PD-L1 positive** NSCLC in adults who have had at least one chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour), only if: • pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression, and • the company provides pembrolizumab in line with the commercial access agreement with NHS England.
TA483[10]	November 2017	Nivolumab	For use within the CDF as an option for treating locally advanced or metastatic squamous NSCLC lung cancer in adults after chemotherapy, only if: • nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and • the conditions in the managed access agreement are followed.
TA484[11]	November 2017	Nivolumab	For use within the CDF as an option for treating locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy, only if: • their tumours are **PD-L1 positive** and • nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and • the conditions in the managed access agreement are followed.

ALK=anaplastic lymphoma kinase; Cancer Drugs Fund; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1

2.2.2 Testing for PD-L1 expression in the NHS

PD-L1 expression is assessed in a laboratory through immunohistochemistry (IHC) staining. The company reports (CS2, p17) that results from a recent analysis conducted for MSD showed that there had been a 5-fold increase in the volume of PD-L1 tests conducted during the period between June and August 2017 (average [redacted] tests per month) compared with the period between September and October 2016 (average [redacted] tests per month).

2.3 Innovation

The company considers that pembrolizumab is an innovative treatment due to its novel mode of action (CS2, p62).

2.4 Number of patients eligible for treatment with pembrolizumab

The company estimates that, in England, 1799 patients would be eligible for treatment with pembrolizumab in 2018. The method used by the company to reach this estimate is described in CS2 (p16).

3 KEYNOTE-024 TRIAL RESULTS

This section provides a structured summary of the clinical effectiveness evidence submitted by the company in support of the use of pembrolizumab for untreated PD-L1 positive metastatic NSCLC. As none of the information on study methodologies, statistical analyses and quality assessment has changed since CS1, the ERG has not included a summary or critique of these aspects in this report. This section focuses on the updated clinical effectiveness results, including adjustments for crossover and adverse events (AEs), from the final analysis of the KEYNOTE-024 trial data.

3.1 Efficacy results from the KEYNOTE-024 trial

Efficacy results from the KEYNOTE-024 trial for the intention-to-treat (ITT) population are summarised in Table 2. The results provided in CS1 were based on the data examined during IA2; the data-cut for IA2 was 9th May 2016. The updated (CS2) results are based on the data examined during the final analysis; the data-cut for the final analysis was 10th July 2017.

Table 2 Results from the KEYNOTE-024 trial (ITT population)

Endpoint	IA2		Final	
	Pembrolizumab N=154	SOC N=151	Pembrolizumab N=154	SOC N=151
Primary endpoint				
PFS (BICR)				
Median, months (95% CI)	10.3 (6.7 to -)	6.0 (4.2 to 6.2)	[redacted]	[redacted]
HR (95% CI)	0.50 (0.37 to 0.68) p<0.001		[redacted]	
Number of events, n (%)	73 (47.4)	116 (76.8)		
Person months	1000.2	785.6		
Event rate/100 person months	7.3	14.8		
PFS rate at 6 months	62.1%	50.3%		
PFS rate at 12 months (95% CI)	47.7%	15.0%	[redacted]	[redacted]
PFS rate at 18 months (95% CI)	NR	NR	[redacted]	[redacted]
PFS rate at 24 months	NR	NR	[redacted]	[redacted]
Secondary endpoints				
OS				
Median, (months) (95% CI)	Not reached	Not reached	30.0 [redacted]	14.2 [redacted]
HR (95% CI)	HR 0.60 (0.41 to 0.89) p=0.005		0.63 (0.47 to 0.86) p=0.002	
Number of events, n (%)	44 (28.6)	64 (42.4)	73 [redacted]	96 [redacted]
Person months	1402	1227.5	[redacted]	[redacted]
Event rate/100 person months	3.1	5.2	[redacted]	[redacted]
OS rate at 6 months	80.2%	72.4%		
OS rate at 12 months (95% CI)	69.9%	54.2%	[redacted]	[redacted]
OS rate at 18 months (95% CI)			[redacted]	[redacted]
OS rate at 24 months (95% CI)			[redacted]	[redacted]
OS rate at 30 months (95% CI)			[redacted]	[redacted]
ORR (BICR)				
Confirmed ORR (95% CI)	44.8% (36.8%to 53%)	27.8% (20.8% to 35.7%)	45.5% (37.4% to 53.7%)	29.8% (22.6 to 37.8)
Difference: pembrolizumab vs SOC (95% CI)	16.6% (6.0% to 27.0%) p=0.0011		14.9% (4.3% to 25.4%) p=0.0031	

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intention to treat; IA2=second interim analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; SOC=standard of care
Source: CS1, Table 17, Table 18, Table 25 and CS2, Table 6, Table 7 and Table 8

The PFS results from the final analyses were similar to the results from the IA2 analyses. Using the final data-cut, median PFS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, [redacted] months versus [redacted] months. In the original ERG report, the ERG noted that there appeared to be a difference of 3.1 months in median PFS between the investigator-assessed results and the results reported for BICR-assessed PFS (7.2 months and 10.3 months respectively). Median PFS in the SOC arm appeared to be similar between the two analyses (5.5 months and 6 months). The ERG is uncertain of the reasons for, or the implications of, the 3.1 months difference between the BICR-assessed PFS and investigator-assessed PFS. No updated investigator assessed PFS data were submitted by the company in CS2.

Using the IA2 data-cut, median OS was not reached. Using the final data-cut, median OS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 30 months versus 14.2 months.

The objective response rate (ORR) results from the final data-cut were similar to the results from the IA2 analyses. Using the final data-cut, the ORR was higher for patients in the pembrolizumab arm compared to patients in the SOC arm (45.5% versus 29.8%), with a confirmed difference in ORR of 14.9% (95% CI 4.3% to 25.4%, p=0.0031).

The results of the exploratory outcomes from the KEYNOTE-024 trial are presented in Table 3 and show that 70 patients in the pembrolizumab arm responded to treatment (median time to response 2.1 months; range, 1.4 to 14.5) and that the median duration of response was not reached in the pembrolizumab arm. In the SOC arm, 45 patients responded to treatment (median time to response 2.2 months; range, 1.8 to 10.3) and the median duration of response was 7.1 months. It is unclear why the upper bound of the time to response range for patients in the SOC arm is lower when calculated using the final dataset than it was when calculated using IA2 data (12.2 months [IA2] versus 10.3 months [final]).

Table 3 KEYNOTE-024 trial exploratory endpoints

Endpoint	IA2		Final	
	Pembrolizumab N=154	SOC N=151	Pembrolizumab N=154	SOC N=151
Time to response (BIRC)				
Number of responders	69	42	70	45
Median (months)	2.2	2.2	2.1	2.2
Range (months)	1.4 to 8.2	1.8 to 12.2	1.4 to 14.5	1.8 to 10.3
Response duration (BIRC)				
Median (months)	Not reached	6.3	Not reached	7.1
Range (months)	1.9+ to 14.5+	2.1+ to 12.6+	1.8+ to 20.6+	2.1+ to 18.1+
Disease control rate				
CR+PR+SD, n (%)	107 (69.5)	102 (67.5)	[redacted]	[redacted]
Progressive disease, n (%)	34 (22.1)	28 (18.5)	[redacted]	[redacted]

BIRC=blinded independent central review; CR=complete response; IA2=second interim analysis; PR=partial response; SD=stable disease; +=censored
Source: CS1, Table 23, Table 24, Table 25 and CS2, Table 15 and Table 16

3.2 Crossover adjustments

The company explained in their response to clarification queries that, at the time of the final analysis, and as allowed in the trial protocol, 54.3% (82/151) of patients in the SOC arm had crossed over to receive pembrolizumab (direct switching). Furthermore, an additional [redacted] 'switch-over events' occurred (indirect switching).

The company carried out four alternative methods to adjust for patient crossover. One set of analyses adjusts for direct switching and the second set of analyses adjusts for both direct and indirect switching (see Table 4). The ERG highlights that the central hazard ratio (HR) results generated by all of the different types of adjustments for direct switching are similar; however, there is greater variation in the central estimates when the different adjustments were made for direct and indirect switching. The ERG has concerns (as described in the TA447 ERG report) relating to the reliability of all the crossover adjustment approaches employed by the company and considers that all results should be viewed with caution.

Table 4 Summary final OS results adjusted for direct and indirect switching

Crossover adjustment method	Pembrolizumab vs SOC					
	Direct switching			Direct and indirect switching		
	HR	95% CI	p-value (2-sided)	HR	95% CI	p-value (2-sided)
ITT	0.63	0.47 to 0.86	0.003	0.63	0.47 to 0.86	0.003
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Simplified two-stage (no re-censoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two-stage (with re-censoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; HR=hazard ratio; IPCW=inverse probability of censoring weighted; ITT=intention to treat; RPSFT=rank preserving structural failure time; SOC=standard of care
* p-value retained from the ITT analysis based on distribution of the test statistic under the null hypothesis of no treatment effect
Source: CS2, Table 9 and Table 10

3.3 Indirect and mixed treatment comparisons

The company offered to update the indirect and mixed treatment comparisons (ITCs and MTCs) that were presented in CS1. However, as new evidence that would ameliorate the concerns expressed in the original ERG report have yet to become available, during the clarification telephone conference, the company, the NICE team and the ERG agreed that updated ITC and MTC results would not be useful to decision-makers.

3.4 Health-related quality of life from the KEYNOTE-024 trial

No new health-related quality of life data from the KEYNOTE-024 trial were submitted as part of CS2.

3.5 Adverse events from the KEYNOTE-024 trial

Clinical advice to the ERG is that AEs arising from treatment with immunotherapy (i.e., pembrolizumab) in patients with NSCLC require careful monitoring. The use of immunotherapies such as pembrolizumab has been evaluated for several years in patients with melanoma; however, in comparison to patients with melanoma, patients with NSCLC are older and have higher rates of co-morbidities. Patients may also have greater variation in available social support. Expert advice to the ERG, presented in the TA447 ERG report, is that a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs is needed at treatment centres in the event that pembrolizumab is approved for use in the treatment of NSCLC in the NHS. Current training of senior and junior oncology medical staff as well as specialist nursing staff may be insufficient to recognise and/or deal with these complications. This approach should be integrated with triage services, and Acute Oncology Units in District General Hospitals.

The ERG has updated the most important TA447 ERG report summaries of AEs with data provided in CS2 (see Table 5); after reviewing these data, the ERG considers that there are no new safety concerns associated with treatment with pembrolizumab in patients with NSCLC. However, the ERG highlights that, for patients treated with pembrolizumab, discontinuations due to AEs and drug-related AEs have increased since the IA2 analyses.

Table 5 Summary of adverse events from the KEYNOTE-024 trial

Adverse event type	IA2		Final	
	Pembrolizumab N=154	SOC N=150	Pembrolizumab N=154	SOC N=150
One or more AE, n (%)	148 (96.1)	145 (96.7)	[redacted]	[redacted]
No AE, n (%)	6 (3.9)	5 (3.3)	[redacted]	[redacted]
Drug related AE, n (%)	113 (73.4)	135 (90.0)	[redacted]	[redacted]
Grade 3 to 5 AE, n (%)	82 (53.2)	109 (72.2)	[redacted]	[redacted]
Grade 3 to 5 drug-related AE, n (%)	41 (26.6)	80 (53.3)	[redacted]	[redacted]
SAE, n (%)	68 (44.2)	66 (44.0)	[redacted]	[redacted]
Serious drug-related AE, n (%)	33 (21.4)	31 (20.7)	[redacted]	[redacted]
Death, n (%)	9 (5.8)	7 (4.7)	[redacted]	[redacted]
Death due to drug-related AE, n (%)	1 (0.6)	3 (2.0)	[redacted]	[redacted]
Discontinued due to AE, n (%)	14 (9.1)	21 (14.0)	[redacted]	[redacted]
Discontinued due to drug-related AE, n (%)	11 (7.1)	16 (10.7)	[redacted]	[redacted]
Discontinued due to SAE, n (%)	13 (8.4)	11 (7.3)	[redacted]	[redacted]
Discontinued due to serious drug-related AE, n (%)	10 (6.5)	7 (4.7)	[redacted]	[redacted]

AE=adverse event; IA2=second interim analysis; SAE=serious adverse event; SOC=standard of care
Source: CS1, Table 41 and CS2, Table 25

4 COST EFFECTIVENESS ANALYSES

4.1 Company economic modelling

The model submitted by the company as part of CS2 is constructed in MS Excel and is identical in structure to the company CS1 model. It is a three-state partitioned survival model, with the three states being PFS, progressed disease and death.

The key elements underpinning the economic modelling presented in CS1 were:

- utility derived from the KEYNOTE-024 trial, differing by a patient's time to death
- effectiveness data for both pembrolizumab and SOC from the KEYNOTE-024 trial with the SOC arm adjusted for patients switching to immunotherapy
- resource use from the KEYNOTE-024 trial and costs from published sources.

The substantive changes to the economic modelling between CS1 and CS2 are:

- use of additional follow up data from the KEYNOTE-024 trial
- use of comparator arm data from the KEYNOTE-024 trial unadjusted for crossover to immunotherapy to model what the company considers to be current NHS care (immunotherapy after progression on chemotherapy).

The CS2 model is essentially the same, algorithmically, as that presented as part of CS1. A minor modification has been made to discounting, namely that, in the CS2 model, discounting is implemented at the start of the second year, rather than from week one, as was the case in the CS1 model. The ERG considers that this change was appropriate and in line with a minor criticism made by the ERG about the CS1 model.

In CS2, the company has provided cost effectiveness results for two scenarios. The only difference between the scenarios is the therapy that patients, whose initial treatment was chemotherapy, receive on disease progression, i.e., either docetaxel (in line with the CS1 base case scenario) or immunotherapy. In CS2, the company makes a robust case that receiving immunotherapy after chemotherapy reflects current NHS practice. It is this cost effectiveness analysis that is the focus of the ERG's critique.

However, the ERG notes that, when considering the first scenario, in the CS2 model, the proportion of patients who initially receive chemotherapy and who receive docetaxel on progression is estimated to be between 2.3% and 9.9%; depending on the methods (adjustment for treatment switching and time point at which a parametric distribution is appended to KEYNOTE-024 trial Kaplan-Meier [K-M] data) used by the company to generate the estimate. The company's updated estimates suggest that their earlier estimate, presented in CS1 (1.9% of patients alive at 5 years), was overly pessimistic. The company's revised

estimate underlines the uncertainties associated with long-term extrapolation of short term data sets and the fact that even a small amount of additional data can alter long-term survival projections.

To generate OS estimates for patients receiving SOC (immunotherapy on disease progression) the company used unadjusted data from the SOC arm of the KEYNOTE-024 trial. Two thirds of patients in this arm ([redacted]) received immunotherapy ([redacted] pembrolizumab and [redacted] other immunotherapies). In the CS2 model, it is assumed that [redacted] of patients receive pembrolizumab and the remaining [redacted] of patients receive docetaxel.

The company has estimated the cost of treatment with pembrolizumab following chemotherapy based on the average number of weeks of treatment received by patients in the SOC arm of the KEYNOTE-024 trial (29.1 weeks). The company's cost of treatment with docetaxel is estimated to be 8.5 weeks. The company state that the source for this assumed length of treatment is TA406 (Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer);[12] however, the rationale for this choice of length of treatment is not provided. Drug and drug administration costs were included in the model as a one-off cost at the time of disease progression.

The company OS estimates (for both patients treated with pembrolizumab and those receiving SOC) were derived by appending exponential distributions to KEYNOTE-024 trial data at three different time points (23, 33 and 43 weeks). The 33-week time point was used in the company base case.

The company's base case results for the comparison of the cost effectiveness of pembrolizumab versus SOC (chemotherapy followed by immunotherapy) are shown in Table 6 (exponential distributions appended to KEYNOTE-024 trial K-M data at 33 weeks). Results generated when exponential distributions are appended to KEYNOTE-024 trial data at 23 and 43 weeks are also provided.

Table 6 Company model results (CS2)

Technologies	Total			Incremental		ICER per QALY gained
	Costs	LYG	QALYs	Costs	QALYs	
Distributions appended to K-M data at 33 weeks (company base case)						
SOC (chemotherapy followed by immunotherapy)	[redacted]	1.86	1.35	-	-	-
Pembrolizumab	[redacted]	3.08	2.31	[redacted]	0.96	[redacted]
Distributions appended to K-M data at 23 weeks						
SOC (chemotherapy followed by immunotherapy)	[redacted]	1.83	1.33	-	-	-
Pembrolizumab	[redacted]	2.99	2.24	[redacted]	0.91	[redacted]
Distributions appended to K-M data at 43 weeks						
SOC (chemotherapy followed by immunotherapy)	[redacted]	1.95	1.43	-	-	-
Pembrolizumab	[redacted]	3.00	2.25	[redacted]	0.83	[redacted]

ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; LYG=life year gained; QALY=quality adjusted life year; SOC=standard of care
Source: CS2 model

4.2 ERG critique of the company economic analysis

4.2.1 Data source for standard of care (pembrolizumab following chemotherapy)

The ERG agrees with the company assessment that, in NHS clinical practice, current care for patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC is chemotherapy followed, on disease progression, by immunotherapy. However, there is currently no trial data that directly compares the efficacy of pembrolizumab in patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC who have, with those that have not, received prior chemotherapy. The company has suggested that as patients in the SOC arm of the KEYNOTE-024 trial were permitted to receive pembrolizumab (or another immunotherapy) following disease progression, these data can be considered to represent outcomes for patients receiving current NHS care.

Examination of the OS K-M data from the SOC arm of the KEYNOTE-024 trial (clarification question B1) reveals that OS for the 54.3% of SOC arm patients who received pembrolizumab following disease progression was much better than that of patients who did not (or had not yet received) an immunotherapy (Figure 1).

Figure 1 SOC arm KEYNOTE-024 trial OS K-M data by treatment switching

The K-M data from the SOC arm of the KEYNOTE-024 trial show that [redacted] patients who did not receive immunotherapy on disease progression died within 6 months of enrolment into the trial compared to [redacted] of SOC arm patients who received immunotherapy. [redacted] receiving pembrolizumab in the SOC arm had died within the first 12 weeks of the trial compared to [redacted] of SOC arm patients who did not receive immunotherapy.

All patients in the SOC arm of the KEYNOTE-024 trial were eligible for immunotherapy following confirmed disease progression. The ERG considers that the high early mortality of patients in the SOC arm who did not receive immunotherapy is evidence that these patients died before, or shortly after disease progression and, therefore, never had the opportunity to receive any subsequent therapy (immunotherapy or docetaxel). The K-M data from the SOC arm of the KEYNOTE-024 trial also show that around [redacted] of patients who did not receive immunotherapy following progression were still alive at [redacted] weeks. These patients were eligible under the trial protocol to receive immunotherapy on disease progression; however, the reasons why they did not do so are unknown. The ERG considers it plausible that at least some of these patients would commence immunotherapy in the future and the potential OS gain from them doing so is not captured by either the OS K-M data from the KEYNOTE-024 trial or any of the current company OS projections.

In the absence of a direct head-to-head trial data comparing the efficacy of pembrolizumab in patients with advanced or metastatic PD-L1 positive (≥50%) NSCLC who are untreated with those previously treated with chemotherapy, the SOC arm for KEYNOTE-024 is currently the best available evidence for this comparison. However, the ERG considers there is evidence

from within the KEYNOTE-024 data that using OS data from the SOC arm of that trial may underestimate the true survival of patients receiving pembrolizumab after chemotherapy.

4.2.2 Pembrolizumab treatment costs

Within the CS2 model, it is assumed that patients who receive pembrolizumab following chemotherapy are prescribed a fixed dose of 200mg every 3 weeks (Q3W). However, it is stated within the [8] issued by the European Medicines Agency that the recommended dose of pembrolizumab for patients with NSCLC who have previously been treated with chemotherapy is 2mg/kg bodyweight Q3W. Applying the cost for the recommended dose of pembrolizumab in the CS2 model (based upon the mean body weight of patients participating in the KEYNOTE-024 trial) reduces the company base case discounted costs for patients receiving SOC by [redacted] to [redacted] per patient, and increases the ICER for the comparison of pembrolizumab versus SOC to [redacted] per QALY gained.

Within the CS2 model, the cost of pembrolizumab, for those who have received prior chemotherapy, was determined by the mean time that patients in the SOC arm of the KEYNOTE-024 trial received pembrolizumab (29.1 weeks). This cost was applied as a one-off fee at disease progression. Given that data from the KEYNOTE-024 trial show that the mean length of time that patients randomised to receive SOC received pembrolizumab following disease progression was 6 months; and the mean time to treatment commencement following disease progression for these patients was 7 weeks, use of discounting in the model would be expected to slightly reduce the total cost of pembrolizumab treatment for these patients. The ERG, therefore, considers that the company's approach to costing treatment with pembrolizumab in patients previously receiving SOC is likely to overestimate the true discounted cost of this treatment. Generating a more accurate cost of treatment would require structural changes to the model that are beyond the remit of the ERG.

4.2.3 Limiting utility values to age-related population norms

In the TA447 ERG report, the ERG highlighted that the utility values in the company model seemed implausibly high for patients with metastatic NSCLC. The utility value in the CS1 and CS2 models for patients who were over 360 days from death was [redacted]. The age-related norm for people aged 65 (the age of the population at model time zero) is 0.79.[13] The ERG made the conservative suggestion that the values used in the company model should be no higher than the age-related population norms. This assumption was accepted by the NICE Appraisal Committee.

The company has undertaken a literature review (CS2, p86-90) and used results from this review to justify using a utility value of [redacted] at 360 days before death in the CS2 model. The ERG considers that results from the company literature review do not strongly support the use of this value as the cited studies either involved patients at slightly different disease stages, were undertaken in countries other than the UK, or involved small numbers of patients. The ERG, therefore, considers that it is appropriate to still limit utility values in the model to be no higher than the age-related population norms.

Adjusting the company base case by model by limiting the utility value to the age-related population norms reduces the difference in QALYs for patients treated with pembrolizumab versus SOC by 0.02 QALYs and increases the ICER for this comparison to [redacted] per QALY gained.

In the TA447 ERG report, the ERG highlighted that alternative (much lower) values for utilities to those used by the company have been used in previous NICE STAs. The ERG has carried out an exploratory analysis involving using utility values reported by Nafees[14] (0.673 for >180 days from death and 0.473 for <180 days from death). The effect on the company base case of using the Nafees utility values is to reduce the difference in QALYs for patients treated with pembrolizumab versus SOC by 0.16 QALYs and increases the ICER for this comparison to [redacted] per QALY gained.

As a point of clarification, the company states in CS2 (p90) 'Additionally and importantly, the NICE reference case stipulates the use of utility values directly derived from the patients.' The ERG highlights that the actual wording of the NICE Reference Case is '…health states drawn from patients directly with societal valuation of these health states.'

4.2.4 Extrapolation of KEYNOTE-024 trial OS data

Within the CS2 model, the company has estimated OS, both for patients initially receiving pembrolizumab and those initially receiving SOC, by appending a variety of parametric distributions to KEYNOTE-024 trial OS K-M data at different time points (23, 33 and 43 weeks). In the TA447 ERG report, the ERG explained that they considered that there was little evidence to support any particular method of extrapolating available trial data. Whilst CS2 includes 6 months more K-M data than CS1, data are still only available for approximately 10% of the model time horizon. The difficulty in choosing the most appropriate curve to use to extrapolate trial data is illustrated by the range of potential distributions considered by the company (see Figure 2 and Figure 3).

Figure 2 Distributions considered by company to extrapolate KEYNOTE-024 trial pembrolizumab arm OS data

Figure 3 Distributions considered by company to extrapolate KEYNOTE-024 trial SOC arm OS data

Visual examination of the various distributions considered by the company to extrapolate KEYNOTE-024 trial pembrolizumab OS data suggest that the company's choice, in their base case, to use an exponential distribution is the joint most pessimistic option; with the projection generated by their Weibull distribution being essentially equivalent to that generated by their exponential distribution. The company also chose, in their base case, to use an exponential

distribution to extrapolate KEYNOTE-024 trial SOC OS data. The exponential distribution is also the most pessimistic of the considered options for extrapolating SOC arm data and leads to a substantially more pessimistic projection than any of the other distributions considered by the company.

Assuming that the same type of distribution is appended to both the pembrolizumab and SOC OS K-M data at 33 weeks, the ICER for the comparison of the cost effectiveness of pembrolizumab versus SOC varies between [redacted] per QALY gained when a generalised-gamma distribution is used to [redacted] per QALY gained when a Weibull distribution is used. The choice of distribution makes a substantial difference to the cost effectiveness of pembrolizumab versus SOC and highlights the uncertainty inherent in the long-term extrapolation of short-term trial data.

During TA428 the company provided evidence from the KEYNOTE-010 trial that, at 5 years between 11.97% and 26.80% of patients receiving pembrolizumab following chemotherapy would be alive; and at 10 years between 2.46% and 24.72% would still be alive. Assuming that the immunotherapies received by the [redacted] of patients in the KEYNOTE-024 trial were all as effective as pembrolizumab in the KEYNOTE-010 trial, it would be expected that, based on the projections provided by the company in their TA428 submission, the CS2 company model projections would show between 7.7 and 17.2% of patients alive at 5 years and between 1.6% and 15.8% alive at 10 years. The CS2 company base case projection suggests 9.1% of patients alive at 5 years (which is within the range previously projected) but the proportion expected to be alive at 10 years is 0.9%, which is much lower than previously estimated. The company's CS2 base case SOC OS projections, therefore, appear pessimistic compared with the company's previous projections.

In addition, the company has not provided any justification for their choice of time-point at which to append any distribution to KEYNOTE-024 trial data. Visual examination of the company's projections generated by appending exponential distributions (the company's base case choice of distribution) to K-M data at 23, 33 and 43 weeks (Figure 4, Figure 5 and Figure 6 respectively) suggests that the closest fit to the trial data occurs when distributions are appended at 43 weeks. There is still an indication from the end of the K-M data (albeit the data becomes heavily censored from week 100) that as this approach generates estimates of 9.6% of patients alive at 5 years and 1.5% alive at 10 years this extrapolation may still underestimate the long-term survival of patients receiving SOC.

Figure 4 OS with K-M exponential extrapolation at 33 weeks (company base case)

Figure 5 OS with KM exponential extrapolation at 23 weeks

Figure 6 OS with KM exponential extrapolation at 43 weeks

The choice of both the distribution used to extrapolate trial data and the time at which the distribution is appended to the K-M data are essentially arbitrary. However, the ERG considers that the distributions that, visually, best fit the data from both arms of the KEYNOTE-024 trial are exponential distributions appended at 43 weeks. The long-term accuracy of the projections for patients in both arms of the trial are, however, unknown.

4.2.5 Treatment stopping at two years

Within the TA447 ERG report, the ERG suggested that some patients may receive pembrolizumab for longer than 2 years, both in the trial and in a real-world setting. As part of the clarification process, the company provided time on treatment data for patients in the KEYNOTE-024 trial who received pembrolizumab (clarification question B1). These data showed (with censoring) that all but one patient had stopped receiving pembrolizumab within 110 weeks (just over two years). However, as there is still only 2 years of follow-up data from the KEYNOTE-024 trial the impact, if any, on the long-term survival of patients who stopped pembrolizumab at 2 years for reasons unrelated to disease status is unclear.

4.3 Impact of ERG amendments on cost effectiveness

In the company CS2 base case, pembrolizumab was estimated to generate an additional 0.96 QALYs at an additional cost of [redacted] compared to SOC (where SOC involves [redacted] of patients receiving immunotherapy following disease progression), with an ICER for the

comparison of the cost effectiveness of pembrolizumab versus SOC of [redacted] per QALY gained.

The ERG has suggested three amendments to the company CS2 model:

1. applying costs associated with the recommended dose of pembrolizumab after progression on chemotherapy
2. limiting the utility values used in the model to be no higher than the population norm
3. applying exponential extrapolations to KEYNOTE-025 OS K-M data from both arms of the trial at 43 weeks.

The impact of the ERG's three amendments on the costs and QALYs of treatment with pembrolizumab and on the ICER per QALY gained are shown in Table 7. Compared to the values generated by the company base case, the ERG's alternative scenario, which involves apply all three amendments, increase the incremental costs of treatment with pembrolizumab by [redacted] per patient and reduces the incremental QALYs by 0.15. These changes increase the size of the company base case ICER from [redacted] to [redacted] per QALY gained.

Details of the revisions made by the ERG to the company CS2 model can be found in Appendix 1

Table 7 ERG adjustments to company base case: pembrolizumab versus SOC (discounted, list prices)

Scenario/ERG amendment	Pembrolizumab			SOC			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1) Cost of pembrolizumab in SOC in line with recommended dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Utility value for >360 days to death set to population norm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) OS extrapolation at 43 weeks for pembrolizumab and SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. ERG alternative scenario (R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year; SOC=standard of care

5 END OF LIFE CRITERIA

Within CS1 (Section 4.13) the company put forward a case that, for the population under consideration, pembrolizumab met NICE's End of Life criteria. However, as the treatment pathway has now changed, and treatment with pembrolizumab following chemotherapy has become a standard of care, the ERG has re-examined the End of Life criterion that patient life expectancy should be less than 24 months.

Median OS of patients in the SOC arm of the KEYNOTE-024 trial is 14.2 months (CS2, p25). The mean life expectancy predicted by the CS2 base case model is 22.3 months (CS2, p13). The ERG's alternative approach to predicting life expectancy, i.e. applying an exponential distribution to KEYNOTE-024 trial OS K-M data at 43 weeks rather than 33 weeks, produces an estimate of mean OS of 23.4 months, which the ERG still considers to be conservative. It is, therefore, not at all certain that the mean life expectancy of the population of interest is less than the 24 months.

6 ERG CONCLUSIONS

Clinical effectiveness

Results, presented in CS2, from analyses of KEYNOTE-024 final data showed that median PFS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 8.5 months versus 6.1 months. In addition, median OS was longer for patients in the pembrolizumab arm compared to patients in the SOC arm, 30 months versus 14.2 months. No new health-related quality of life data were provided from the KEYNOTE-024 trial and there were no new safety concerns.

Cost effectiveness

The ERG suggested three amendments to the CS2 model base case:

1. applying the costs associated with the recommended dose of pembrolizumab after progression on chemotherapy
2. limiting the utility values used in the model to be no higher than the population norms
3. applying exponential extrapolations to KEYNOTE-025 trial OS K-M data, from both arms of the trial, at 43 weeks

Applying costs for the recommended dose of pembrolizumab following chemotherapy makes costs more relevant to the NHS.

The ERG considers that the amendment to the utility value provides a more accurate, but still optimistic, projection of the likely quality of life of patients with metastatic NSCLC.

In terms of OS, with trial data only available to populate 10% of the model time horizon (20-years), all survival projections, both for treatment with pembrolizumab and for treatment with SOC, are highly speculative. The ERG highlights that evidence from the KEYNOTE-010 trial suggests that the company's base survival projection for patients receiving SOC may be pessimistic. This casts doubt not only on the ICER for the comparison of the cost effectiveness of treatment with pembrolizumab versus SOC, but also on whether pembrolizumab should be considered as an end of life treatment.

7 REFERENCES

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8 APPENDICES

Appendix 1 ERG Revisions to the CS2 company model

ERG Section 6 results table revision	Implementation instructions
R1. Cost of pembrolizumab in SOC in line with recommended dose	In Sheet 'Regimen Costs UK' Set formula in cell c125= (J22*2*'Model Inputs'!E21*(1-s.PAS.Before.Pembro))/3
R2. Utility value for >360 days to death set to population norm	In Sheet 'utility inputs' Set value in cell D15=0.79 Set value in cell E15=0.79
R3. OS extrapolation at 43 weeks for pembrolizumab and SOC	In Sheet 'Model Settings' Set value in Drop Down 40="Week 43"