NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer

1 Recommendations

1.1 Cemiplimab with platinum-based chemotherapy should not be used for untreated non-small-cell lung cancer (NSCLC) in adults when the cancer:

- is locally advanced and not suitable for definitive chemoradiation, or metastatic
- has PD-L1 in 1% or more of the tumour cells and
- has no EGFR, ALK or ROS-1 aberrations.

1.2 This recommendation is not intended to affect treatment with cemiplimab with platinum-based chemotherapy that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Cemiplimab with platinum-based chemotherapy is not required to be funded in the NHS in England for untreated NSCLC in adults when the cancer:

- is locally advanced and not suitable for definitive chemoradiation, or metastatic
- has PD-L1 in 1% or more of the tumour cells and
- has no EGFR, ALK or ROS-1 aberrations.

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It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest cemiplimab with platinum-based chemotherapy is value for money.

Why the committee made these recommendations

Usual treatment for advanced NSCLC includes chemotherapy alone, immunotherapy alone, or immunotherapy plus chemotherapy. Cemiplimab is a type of immunotherapy.

For this evaluation, the company asked for cemiplimab plus chemotherapy to be considered only for people who would otherwise be offered pembrolizumab plus chemotherapy. This does not include everyone who it is licensed for.

Clinical trial evidence shows that cemiplimab plus chemotherapy increases how long people have before their cancer gets worse and how long they live compared with placebo plus chemotherapy. Cemiplimab plus chemotherapy has not been directly compared in a clinical trial with pembrolizumab plus chemotherapy. The results of indirect comparisons are uncertain.

There are concerns with the economic model. This is mainly because of the way the company structured its model.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for cemiplimab plus chemotherapy. And the cost-effectiveness estimates preferred by the company and the external assessment group are above the range normally considered an acceptable use of NHS resources. So it should not be used.

2 Information about cemiplimab

Marketing authorisation indication

2.1 Cemiplimab (Libtayo, Regeneron) with platinum-based chemotherapy is indicated for 'the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- metastatic NSCLC'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cemiplimab.

Price

2.3 The list price of cemiplimab is £4,650 for a vial of 350 mg per 7 ml concentrate for solution for infusion (excluding VAT; BNF online accessed February 2025).

2.4 The company has a commercial arrangement. This makes cemiplimab available to the NHS with a discount and it would have also applied to this indication if cemiplimab had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on the company website under the UK Baseline Emissions Footprint & Carbon Reduction Plan.

3 Committee discussion

The evaluation committee considered evidence submitted by Regeneron, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Non-small-cell lung cancer (NSCLC) is staged from 1A to 4B according to the size of the tumour, location of involved lymph nodes and the presence of distant metastases. When NSCLC is diagnosed as stage 3 (locally advanced) or stage 4 (metastatic), it is considered advanced. People with locally advanced NSCLC commonly present with a cough. Other symptoms include shortness of breath, coughing up blood, and pain. People with metastatic NSCLC may also have headaches, an enlarged liver, changes in mental health, weakness and seizures. The patient expert submission noted that symptoms of untreated, advanced NSCLC can be debilitating and distressing for loved ones to observe. The committee concluded that advanced NSCLC can substantially affect health-related quality of life.

Clinical management

Treatment options

3.2 Treatment for lung cancer is defined by histology (non-squamous or squamous NSCLC) and PD-L1 expression. This is in line with NICE's guideline on lung cancer: diagnosis and management. First-line treatment options for advanced squamous NSCLC for tumours that express PD-L1 at less than 50% with no targetable mutations are:

- pembrolizumab plus carboplatin and paclitaxel (see NICE technology appraisal guidance 770 [TA770])
- platinum doublet chemotherapy.

First-line treatment options for advanced squamous NSCLC for tumours that express PD-L1 at 50% or more with no targetable mutations are:

- pembrolizumab plus carboplatin and paclitaxel, if urgent clinical intervention is needed (TA770)
- pembrolizumab alone (NICE technology appraisal guidance 531 ([TA531])
- atezolizumab alone (NICE technology appraisal guidance 705 [TA705])
- platinum doublet chemotherapy.

First-line treatment options for advanced non-squamous NSCLC for tumours that express PD-L1 at less than 50% with no targetable mutations are:

- pembrolizumab plus pemetrexed and platinum chemotherapy (NICE technology appraisal guidance 683 [TA683])
- platinum doublet chemotherapy
- pemetrexed plus cisplatin (NICE technology appraisal guidance 181 [TA181]
- pemetrexed with carboplatin
- atezolizumab plus bevacizumab, carboplatin and paclitaxel (NICE technology appraisal guidance 584 [TA584]).

First-line treatment options for advanced non-squamous NSCLC for tumours that express PD-L1 at 50% or more with no targetable mutations are:

- pembrolizumab plus pemetrexed and platinum chemotherapy (TA683)
- pembrolizumab alone (TA531)
- atezolizumab alone (TA705)
- pemetrexed plus platinum chemotherapy.

Target population and comparators

3.3 The company positioned cemiplimab plus chemotherapy as a treatment for advanced PD-L1-positive (that is, tumours that express PD-L1 at 1% or more) NSCLC with no targetable mutations in adults who would otherwise be offered treatment with immunotherapy plus chemotherapy. This is a narrower population than is covered by the marketing authorisation, which does not specify 'would otherwise be offered treatment with immunotherapy plus chemotherapy' (see section 2.1). Based on its chosen target population, the company included only pembrolizumab plus chemotherapy as a comparator in its submission. The company stated that its choice of target population and comparator was because there are clinical differences between people for whom combination treatment is suitable (that is, immunotherapy plus chemotherapy) and people who would have immunotherapy or chemotherapy alone. It explained that chemotherapy alone is generally limited to people who have contraindications to immunotherapy, and so it did not believe chemotherapy alone to be a relevant comparator. It also stated that immunotherapy plus chemotherapy is used to help achieve a rapid response so the person can subsequently benefit from immunotherapy. So, combination treatment would be used in different clinical scenarios to immunotherapy alone. So, the company also did not believe pembrolizumab monotherapy or atezolizumab monotherapy were relevant comparators. The clinical experts added that they try to avoid prescribing chemotherapy if possible because of toxicity. But if symptoms are progressing, chemotherapy may be needed as well as immunotherapy to achieve a response. They agreed with the company that combination treatment would be used in different clinical scenarios to immunotherapy monotherapy.

The company acknowledged that atezolizumab combination therapy is recommended for non-squamous NSCLC tumours that express PD-L1 at 1% to 49%. But it did not think this was a relevant comparator because it only has an approximately 8% market share in this subpopulation. The

NHS England Cancer Drugs Fund (CDF) clinical lead (from here, CDF lead) clarified that only about 2% of people in this subpopulation have atezolizumab combination therapy.

The EAG agreed that based on the company's target population, pembrolizumab plus chemotherapy was the only suitable comparator. It noted that for people with squamous NSCLC whose tumours express PD-L1 at 50% or more, pembrolizumab plus chemotherapy is recommended only if urgent clinical intervention is needed. The committee agreed that if cemiplimab were recommended, it would include the same criterion in the recommendation. The CDF lead and clinical experts agreed that pembrolizumab plus chemotherapy was the only relevant comparator for this evaluation. The clinical experts stated that it was challenging to describe the company's target population according to defined criteria. But healthcare professionals are experienced in identifying people for whom immunotherapy plus chemotherapy is suitable. The CDF lead confirmed that Blueteq forms would be used in NHS practice, to help healthcare professionals identify the target population for cemiplimab plus chemotherapy. They added that although pembrolizumab plus chemotherapy is licensed for untreated PD-L1 positive or PD-L1 negative metastatic NSCLC, it is also commissioned in the NHS for locally advanced disease. But cemiplimab plus chemotherapy is licensed only for advanced NSCLC that is PD-L1 positive. The committee noted that evidence for cemiplimab's clinical and cost effectiveness was based on untreated PD-L1 positive NSCLC (see sections 3.6 and 3.7). This aligned with the population who could have cemiplimab plus chemotherapy. The committee was satisfied that the company's target population could be identified by healthcare professionals in the NHS and so concluded it was an appropriate population. The committee further concluded that, for the company's target population, pembrolizumab plus chemotherapy was the only appropriate comparator.

Combination chemotherapy regimens

3.4 The chemotherapy regimens used in combination with immunotherapies in UK practice are specified in the Bluteq protocol. For non-squamous NSCLC, the chemotherapy option is pemetrexed with platinum-based chemotherapy. For squamous NSCLC, the chemotherapy regimens are carboplatin and paclitaxel. In the EMPOWER-Lung 3 trial (see section 3.5), of those randomised to the cemiplimab plus chemotherapy arm, most people with squamous NSCLC had cemiplimab with paclitaxel and carboplatin or cisplatin. Most people with non-squamous NSCLC that were randomised to the cemiplimab plus chemotherapy arm had cemiplimab with pemetrexed and carboplatin or cisplatin. Approximately one-fifth had cemiplimab with a pemetrexed-free chemotherapy regimen. The company noted that for people with non-squamous NSCLC, pembrolizumab must be given in combination with pemetrexed (and platinum-based chemotherapy). But, in EMPOWER-Lung 3, people with non-squamous NSCLC could have chemotherapy without pemetrexed, which the company believed allowed greater flexibility of chemotherapy treatment (see section 3.17). The company noted that it was not possible to estimate the proportion of people that would have cemiplimab without pemetrexed in clinical practice or their characteristics because of heterogeneity across England and Wales. The committee noted that chemotherapy regimens given in combination with pembrolizumab in clinical practice may differ from the chemotherapy regimens given in combination with cemiplimab in clinical practice, if cemiplimab were recommended. But it was uncertain what proportion of people with non-squamous NSCLC would have cemiplimab without pemetrexed in clinical practice, or if EMPOWER-Lung 3 reflected this.

Clinical effectiveness

EMPOWER-Lung 3, part 2

3.5 The clinical evidence for cemiplimab with platinum-based doublet chemotherapy came from part 2 of the EMPOWER-Lung 3 trial. This was

a phase 3, randomised, double-blind, placebo-controlled superiority trial. It compared cemiplimab plus platinum-based doublet chemotherapy with placebo plus platinum-based doublet chemotherapy in adults with untreated advanced squamous or non-squamous NSCLC with no targetable mutations. The trial recruited people regardless of PD-L1 expression, but the company submission focused on people whose tumours expressed PD-L1 at 1% or more to align with the marketing authorisation (from here, referred to as the Medicines and Healthcare products Regulatory Agency [MHRA] label population; n=327). The trial was stopped early on the recommendation of an independent data monitoring committee because of superior overall survival. This data cut (June 2022) represented approximately 28 months of follow up and showed a statistically significant difference in overall and progression-free survival in favour of cemiplimab plus chemotherapy compared with placebo plus chemotherapy. In the MHRA label population, median overall survival was 23.5 months for cemiplimab plus chemotherapy and 12.1 months for placebo plus chemotherapy (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.38 to 0.69). Median progression-free survival was 8.3 months for cemiplimab plus chemotherapy and 5.5 months for placebo plus chemotherapy (HR 0.48, 95% CI 0.37 to 0.62). The company also presented subgroup analyses based on histology and PD-L1 expression status. The improvements in overall survival and progression-free survival in favour of cemiplimab plus chemotherapy were statistically and clinically significant in all subgroups except for overall survival in the squamous, PD-L1 50% or more subgroup. The committee thought that the trial stopping early may have resulted in the treatment effect being overestimated. It concluded that treatment with cemiplimab plus chemotherapy resulted in clinically meaningful improvement in overall and progression-free survival compared with chemotherapy alone.

Indirect treatment comparisons

Network meta-analyses

3.6 Because there was no direct evidence comparing cemiplimab plus chemotherapy with pembrolizumab plus chemotherapy, the company compared them indirectly and presented network meta-analyses (NMAs) in its submission. The base-case efficacy analysis comprised a population with PD-L1 expression at 1% or more with squamous or non-squamous histology, in line with the MHRA label population. To inform the clinical effectiveness of pembrolizumab plus chemotherapy, the company used data from 2 trials:

- KEYNOTE-189, a phase 3 trial comparing pembrolizumab plus pemetrexed and platinum chemotherapy with placebo plus pemetrexed and platinum chemotherapy in people with untreated metastatic non-squamous NSCLC
- KEYNOTE-407, a phase 3 trial comparing pembrolizumab plus paclitaxel and carboplatin with placebo plus paclitaxel and carboplatin in people with untreated metastatic squamous NSCLC.

The company had access to patient-level data from EMPOWER-Lung 3 but only aggregate data from the KEYNOTE trials. For the progression-free survival and overall survival outcomes, the company did a 2-step NMA (outlined by Cope et al. [2020]), which allowed for hazard ratios to vary over time. It chose this approach because the proportional hazards assumption was likely violated for some outcomes. The company chose fixed effect models for all analyses. It presented time-varying hazard ratios for cemiplimab plus chemotherapy compared with pembrolizumab plus chemotherapy at 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months and 36 months. For overall survival, the point estimate hazard ratios were below 1 (that is, they favoured cemiplimab plus chemotherapy) at all time points but were not statistically significant. For progression-free survival, the point

estimates were 1 or above at all time points (that is, they favoured pembrolizumab plus chemotherapy), and were not statistically significant. The company said that these analyses suggested there were no meaningful differences in efficacy between cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. It added that this was in line with clinical expert opinion and clinical guidelines

The committee noted that the results not being statistically significantly different did not equate to the treatments being equivalent in efficacy or non-inferior. The company acknowledged that the credible intervals were wide and that there were limitations with the NMA. NMAs are based on the assumption of sufficient clinical and methodological similarity (homogeneity) between the included studies, across all comparisons. This means they can be assumed to estimate the same (or similar) relative treatment effect, regardless of which treatments are actually included in each study. KEYNOTE-189 and KEYNOTE-407 included people irrespective of PD-L1 expression, and baseline characteristics were not reported according to PD-L1 expression status. So, the company assumed similarity in treatment effect modifiers between the KEYNOTE trials and EMPOWER-Lung 3.

The EAG noted that the analysis had no closed loops, which meant that it was not possible to assess the validity of the assumption of sufficient similarity across studies making different comparisons. Another limitation noted by the EAG was that the KEYNOTE trials allowed crossover from the control to the intervention arm at disease progression, but the effects of crossover on overall survival were not adjusted for in the company's base-case NMA presented at the first committee meeting. At 5 years in the KEYNOTE studies, approximately 41% of people had crossed over to the pembrolizumab plus chemotherapy arm. In contrast, EMPOWER-Lung 3 did not allow for crossover at disease progression. The EAG thought that this may

favour cemiplimab plus chemotherapy in the NMA because crossover in the KEYNOTE trials may have diluted the overall survival treatment effect for pembrolizumab plus chemotherapy. The committee thought that without crossover-adjusted results, the impact of crossover in the KEYNOTE studies added uncertainty to the NMA results for overall survival.

In response to draft guidance consultation, the company presented a scenario including crossover-adjusted overall survival data from KEYNOTE-407 (squamous population) in its NMA. No crossover-adjusted data was available for KEYNOTE-189 (non-squamous population). The company noted the point estimate hazard ratios increased (became less favourable to cemiplimab) when using the crossover-adjusted data. But it said the confidence intervals for hazard ratios included 1 at all time points and still demonstrated similar overall survival between cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. The committee noted that baseline characteristics specifically for people whose tumours expressed PD-L1 at 1% or more were not available for the KEYNOTE trials. But it noted that there were other potential treatment effect modifiers that differed between EMPOWER-Lung 3 and the KEYNOTE trials. These included:

- duration of treatment
- distribution of PD-L1 expression
- age
- performance status
- cancer stage at diagnosis
- smoking history
- study site locations (potential differences in healthcare resource use)
- treatments offered at second line and beyond.

The committee highlighted that these could affect progression-free survival or overall survival outcomes or both. It was also concerned that

the differences in these variables between the trials increased uncertainty in the validity of the assumption of sufficient similarity across studies. The committee also recalled that the company's base-case NMA did not adjust for crossover, and the impact of crossover in the KEYNOTE-189 study remained in the scenario analysis. It concluded that the NMA results were highly uncertain, especially for overall survival.

Matching-adjusted indirect comparisons

3.7 In response to the draft guidance consultation, the company did anchored matching-adjusted indirect comparisons (MAICs) to address the differences in the baseline characteristics between the key trials. Covariates included in the base-case MAICs included PD-L1 expression, age, smoking status and Eastern Cooperative Oncology Group (ECOG) score. The company included scenarios exploring the impact of including additional covariates in the MAICs, including brain metastases and ethnicity. The non-squamous histology subgroup with PD-L1 expression of 1% or more from EMPOWER-Lung 3 was matched to the intention-to-treat population (any PD-L1 expression level) from KEYNOTE-189. The squamous histology subgroup with PD-L1 expression of 1% or more from EMPOWER-Lung-3 was matched to the intention-to-treat population (any PD-L1 expression level) from KEYNOTE-407. The company also did scenario analyses using the intention-to-treat (any PD-L1 expression level) populations from both the EMPOWER-Lung 3 and KEYNOTE trials. The company only incorporated published crossover-adjusted data from the KEYNOTE-407 trial into the MAIC. It stated that this was because of a lack of published crossover-adjusted data for the KEYNOTE-189 trial (non-squamous histology). It noted that the NICE technology appraisal guidance for pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC (TA557, now replaced by TA683) reported that crossover adjustment had little effect on the results. But the company acknowledged that this analysis had only been done in a population that would not be eligible for pembrolizumab.

At the first meeting, the committee recognised that the KEYNOTE trials had longer post-progression follow-up data available than the EMPOWER-Lung 3 trial. So, the data on overall survival for pembrolizumab plus chemotherapy was more mature and less uncertain. It recalled that EMPOWER-Lung 3 was stopped early because of superior overall survival with cemiplimab (see section 3.5), which was potentially associated with a bias favouring cemiplimab plus chemotherapy. In contrast, the KEYNOTE trials did not end early, to the committee's knowledge. The committee thought that this contributed to the uncertainty in the NMA (see section 3.6). In response to draft guidance consultation, the company included MAICs using data from a 2-year follow-up period common to the EMPOWER-Lung-3 and KEYNOTE trials, and did MAICs using the extended follow-up data from the KEYNOTE trials. The company said the MAICs using the 2 follow-up periods did not change the results substantially. The EAG thought that the company's approach would have removed any potential bias associated with the different follow-up times.

The company said that a limitation of the MAICs was that a constant hazard ratio was estimated for each data set, but that the proportional hazards assumption was violated for some outcomes. The company said that the results of the MAICs were consistent with the results from its original NMA (see section 3.6) and further supported its conclusions that there was no meaningful difference in efficacy between cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. The EAG noted that although the company followed established methods to adjust for crossover, these methods are generally limited in their robustness. It added that there was still uncertainty about the relative effectiveness of cemiplimab plus chemotherapy compared with pembrolizumab plus chemotherapy.

The committee noted that by matching to the populations of the KEYNOTE trials, the MAIC populations no longer reflected the EMPOWER-Lung-3 trial population. The company acknowledged that EMPOWER-Lung 3 was more generalisable to NHS clinical practice than the KEYNOTE trials because use of immunotherapy after progression in the placebo plus chemotherapy arm of the EMPOWER-Lung 3 trial better reflected NHS practice. The committee was concerned that the relative treatment effect estimated by the MAICs may not have been generalisable to NHS clinical practice. It was also concerned that the MAIC in the company's model appeared to increase the incremental quality-adjusted life years (QALYs). It recalled that crossover in the KEYNOTE trials diluted the overall survival treatment effect for pembrolizumab plus chemotherapy and so using the MAIC with crossover-adjusted data in the model was expected to improve outcomes for pembrolizumab plus chemotherapy. The company explained that ECOG status could not be matched for in the MAIC with KEYNOTE-407 because of low numbers of people with an ECOG score of 0 in EMPOWER-Lung 3. The company said that although adjusting for crossover improved the overall survival hazard ratios for pembrolizumab plus chemotherapy, adjusting for ECOG status improved the hazard ratios for cemiplimab plus chemotherapy. The committee recalled its conclusion that the NMA results were highly uncertain, especially for overall survival (see section 3.6). It appreciated that the company had presented indirect treatment comparison results using crossover-adjusted data from KEYNOTE-407. But it remained concerned that the data from KEYNOTE-189 was not adjusted for crossover. The committee recalled that indirect treatment comparison results not being statistically significantly different did not equate to the treatments being equivalent in efficacy or non-inferior (see section 3.6). It concluded that the results of the MAIC were highly uncertain and did not resolve its concerns with the results of NMAs.

Economic model

Model structure

3.8 The company provided a 3-state partitioned survival model, with a 30-year time horizon. In its base case, it applied estimates of treatment effects from the 2-step NMA to the shape and scale parameters of the reference curve (EMPOWER-Lung 3 chemotherapy arm) to generate progression-free survival and overall survival curves for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. The EAG thought the model structure was appropriate. The committee noted that the incremental QALY gain for cemiplimab plus chemotherapy predicted by the company's modelling primarily resulted from the NMA hazard ratio point estimates favouring cemiplimab plus chemotherapy for overall survival. But it recalled that it thought the NMA results were highly uncertain, and that overall survival was potentially biased in favour of cemiplimab plus chemotherapy (see section 3.6). So, the partitioned survival model structure may have been biased in favour of cemiplimab plus chemotherapy, because overall survival was modelled independently of progression-free survival. The committee would have expected post-progression survival to be similar for people who had cemiplimab plus chemotherapy and people who had pembrolizumab plus chemotherapy. This is because in NHS clinical practice, the same treatment options would be available to both groups after progression. So, at the first meeting the committee requested to see a Markov model structure based on progression-free survival data from the NMA, with the assumption of equal mortality risk after progression for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy.

The company did not provide the model requested by committee in response to consultation and instead provided MAICs (see section 3.7) that had not been requested. The company said that partitioned survival models are a well-established approach to modelling treatments in previous appraisals in NSCLC. At the second committee meeting, the

company verbally stated that according to a publication that compared Markov models to partitioned survival models, Markov models are not appropriate unless individual patient data is available for both treatment arms. But it did not state this or provide a reference to the publication in its response to the draft guidance. The company said it had provided MAICs to address the committee's uncertainty about the comparative effectiveness of cemiplimab and pembrolizumab in terms of progression-free survival; it expected that this, alongside a scenario assuming no difference in overall survival between cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy, would mitigate the need to provide a Markov state transition model. The company explained that the results of its indirect treatment comparisons showed no meaningful differences in effectiveness between cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy (see sections 3.6 and 3.7), and that this supported a cost-comparison approach, which it had provided as an alternative to its cost–utility analysis. The company said this was further supported by precedent in previous technology appraisals in non-small-cell lung cancer of comparing treatment costs in the absence of evidence of a meaningful difference in effectiveness between immunotherapies, such as TA705. But the committee for TA705 had thought that the company took a conservative approach to modelling cost effectiveness, modelling a QALY loss and cost savings in its base case. The committee noted it had not been presented with a similar analysis, or an analysis reflecting its preferred approach (a progression-free survival-driven Markov model), in this evaluation. It recalled that indirect treatment comparison results not being statistically significantly different did not equate to the treatments being equivalent in efficacy or non-inferior (see section 3.6). The committee also noted that the results of the company's scenario assuming no difference in overall survival between cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy were substantially above what NICE considers a cost-effective use of NHS resources.

The committee concluded that the evidence for clinical similarity was not robust enough for a cost-comparison analysis. It further concluded that the partitioned survival model structure may not provide reliable cost-effectiveness estimates and that it had not been provided with a Markov model structure as requested to explore its concerns.

Time to treatment discontinuation

3.9 The EMPOWER-Lung 3 protocol allowed people to continue having cemiplimab after disease progression. The company stated that in this trial, most people did not have access to post-progression second-line immunotherapy treatments, which likely led to staying on cemiplimab longer than they would have otherwise. But the marketing authorisation for cemiplimab differs from the trial protocol and specifies that cemiplimab treatment 'may be continued until disease progression or unacceptable toxicity'. Based on this and clinical expert opinion, the company did not anticipate that treatment would continue after disease progression in clinical practice. So, it assumed that time on treatment was equal to progression-free survival for cemiplimab plus chemotherapy. The same assumption also applied for pembrolizumab plus chemotherapy. The company also provided a scenario analysis in which a ratio was applied to the progression-free survival curve to generate the time-on-treatment curve. For EMPOWER-Lung 3, the ratio was estimated using a Cox model. But the company noted that this ratio should be interpreted with caution, because the underlying assumption of independence of groups was violated. For pembrolizumab plus chemotherapy, the company estimated the weighted ratio from the median progression-free survival time and median time on treatment reported in the KEYNOTE studies, using an exponential distribution. This resulted in estimated ratios (for time on treatment compared with progression-free survival) of 1.17 for cemiplimab plus chemotherapy and 0.84 for pembrolizumab plus chemotherapy (a ratio above 1 indicated longer time on treatment than progression-free survival). The company stated that healthcare

professionals at an advisory board meeting said that differences in time on treatment between pembrolizumab and cemiplimab may be because of 'immunotherapy experience bias or reporting variations between trials'.

The EAG noted that assuming that time on treatment was equal to progression-free survival ignored that time on treatment affects progression-free survival and overall survival. It thought that this assumption underestimated the costs for cemiplimab plus chemotherapy and overestimated the costs for pembrolizumab plus chemotherapy. In its base case, the EAG used the ratios calculated by the company to estimate the time-on-treatment curves for cemiplimab and pembrolizumab. The committee agreed with the EAG that time on treatment affects progression-free survival and overall survival. It thought that there was uncertainty about the impact on overall survival of treatment after progression. It also noted there was uncertainty about the impact on progression-free survival and overall survival of continued treatment beyond the protocol-defined 108 week stopping rule (see section 3.10). The committee noted that the summary of product characteristics states that cemiplimab should be used 'until disease progression or unacceptable toxicity'. It was mindful that it could only make recommendations within the marketing authorisation. The committee noted that cemiplimab was given after disease progression in EMPOWER-Lung 3. It noted that it was important to align modelled costs and benefits. The committee decided that it would be appropriate to use time-on-treatment data directly from EMPOWER-Lung 3 and the KEYNOTE trials. It acknowledged that the company did not have access to Kaplan–Meier data for time on treatment from the KEYNOTE studies. So it concluded at the first meeting that it preferred the ratio method to calculate time on treatment for pembrolizumab (until the stopping rule was applied; see section 3.10) rather than assuming time on treatment was equal to progression-free survival. For cemiplimab, it requested further analyses using the time-on-treatment Kaplan–Meier data from

EMPOWER-Lung 3, either directly or using the best fitting parametric survival model fitted to that data, as per the NICE Decision Support Unit's technical support document 14. It said that this should also include treatment costs for people who continued treatment beyond 108 weeks (see section 3.10).

In response to consultation, the company explained that, given its use of adjusted survival data for cemiplimab which was not aligned with the observed time on treatment, it did not model time on treatment using the EMPOWER-Lung 3 Kaplan–Meier data as requested. At the second committee meeting, it added that it was not appropriate to use the Kaplan–Meier data for cemiplimab. This was because Kaplan–Meier data and the shape of a respective Kaplan–Meier curve were not available to similarly model pembrolizumab time on treatment, so this would likely introduce bias. So the company retained its approach of assuming that time on treatment was equal to progression-free survival for both treatment arms in its base case. The committee recalled its conclusions from the first committee meeting. It concluded that it had not been presented with analyses that reflected its preferred approach for modelling time on treatment, which was the ratio method for pembrolizumab and using Kaplan–Meier data from EMPOWER-Lung 3 for cemiplimab.

Stopping rule

3.10 The company's model included a 2-year stopping rule for cemiplimab. This rule is not stated in the summary of product characteristics for cemiplimab. The company stated that it chose this stopping rule in line with guidance for pembrolizumab plus chemotherapy in TA683 and TA770. It added this was also in line with EMPOWER-Lung 3, in which the protocol allowed treatment for a maximum of 108 weeks. The CDF clinical lead stated that in clinical practice, pembrolizumab treatment given every 3 weeks is stopped after 35 cycles. The EAG stated that the company modelled the stopping rule for cemiplimab and pembrolizumab such that treatment stopped at 2 calendar years. The committee noted that this

differed to how the stopping rule for pembrolizumab is implemented in NHS practice. It also noted that, based on Kaplan–Meier time-to-treatment-discontinuation data, some people in EMPOWER-Lung 3 appeared to have continued treatment beyond the protocol-defined maximum of 108 weeks; at approximately 27 months, 42 people were still having cemiplimab. At the first committee meeting, the committee requested that the stopping rule for cemiplimab in the model should reflect the EMPOWER-Lung 3 protocol. For pembrolizumab, the committee requested that the company update the stopping rule in the model to reflect NHS practice (that is, 35, 3-weekly cycles).

In response to consultation, the company updated its stopping rules to align with the committee's preferences. It explained that treatment with cemiplimab appeared to continue beyond 108 weeks in the EMPOWER-Lung-3 trial because of dose delays (occurring in 51% patients), and that no more than the maximum of 36 doses were given, equivalent to 108 weeks. The company further explained that some people in the KEYNOTE trials were similarly reported as having remained on pembrolizumab treatment beyond the maximum 2-year treatment duration specified in the study protocols. It also noted that there was a lack of evidence that continued immunotherapy use results in improved outcomes compared with fixed-duration immunotherapy for the population of interest. The committee noted that the stopping rule for cemiplimab was reported as a maximum of 36 doses in the consultation response but a treatment period of 108 weeks in the company submission and publications for the EMPOWER-Lung 3 trial. It said this added to the uncertainty about the appropriate stopping rule for cemiplimab. The company explained that a maximum of 36 doses of cemiplimab given over 108 weeks was in line with the trial protocol, assuming no dose pauses. It noted that treatment periods extending beyond trial protocol stopping rules was a result of dose pauses, which were expected to affect the KEYNOTE trials as well as EMPOWER-Lung 3. The committee concluded

that the company's updated modelling of the stopping rules was appropriate.

Waning of treatment effect after stopping treatment

3.11 For both cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy, the company assumed that the treatments continued to be effective after stopping treatment and so continued extrapolation of the treatment effect from year 2 to year 5. At year 5, the hazard of progression and death was assumed to immediately equal the hazard of progression and death for the placebo plus platinum-based doublet chemotherapy arm of the EMPOWER-Lung 3 trial. The company claimed that the 5-year waning time point was supported by 5-year follow-up data from KEYNOTE-189 and KEYNOTE-407 which demonstrated a continued benefit after stopping treatment. It added that this assumption was also supported by clinical experts that the company consulted, who stated that it was reasonable to generalise follow-up data for pembrolizumab to cemiplimab. The clinical experts also stated that people continue to benefit after 2 years of immunotherapy treatment because of T-cell activation through 3 to 5 years.

The EAG thought that the company's assumption of an immediate waning of treatment effect at 5 years overestimated the treatment effect for both cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. It also thought that applying waning on an immediate basis did not reflect the mechanism of action of immunotherapies and lacked face validity. For its base case, it assumed a gradual waning of treatment effect for both treatments. Specifically, it assumed a gradual waning of treatment effect starting at 2 years and ending at 5 years, at which point the hazard of progression and death for both treatments equalled that of placebo plus platinum-based doublet chemotherapy.

The company had not provided any analysis of 5-year follow-up data from KEYNOTE-189 and KEYNOTE-407 to support its assumption of a 5-year

treatment waning time point. At the first meeting, the committee concluded that it preferred a gradual approach to treatment waning, rather than an immediate waning of treatment effect. It further concluded that the long-term treatment effect of cemiplimab plus chemotherapy was uncertain. The committee requested further justification from the company to support a 5-year waning time point; for example, estimates of the hazards over time from the longer-term data from the KEYNOTE-189 and KEYNOTE-407 trials compared with the modelled hazards. It also requested further evidence to support a 5-year waning time point based on data specifically for cemiplimab plus chemotherapy.

In response to consultation, the company updated its base case to align with the committee's preference for gradual waning of treatment effect for both arms, applied from 3 to 5 years. It also provided a comparison of the modelled hazard rates over time compared with hazards from KEYNOTE-189 and KEYNOTE-407. The company said that the hazards decreased up to the end of follow up for overall survival and progression survival, and so the EAG's application of waning from 2 to 5 years was conservative. The EAG noted that the hazards were highly uncertain and did not show the change in relative effectiveness over time. The company did not provide the requested evidence to support a 5-year waning time point for cemiplimab plus chemotherapy because of the early stopping of EMPOWER-Lung-3. It instead presented evidence from the 5-year follow up from EMPOWER-Lung 1, a trial for cemiplimab monotherapy compared with chemotherapy in advanced or metastatic NSCLC with PD-L1 expression at 50% or more. The company said the evidence suggested the assumption of treatment benefit for cemiplimab plus chemotherapy lasting for up to 5 years was reasonable. The committee recalled that clinical experts had said that people continue to benefit after 2 years of immunotherapy treatment because of T-cell activation through 3 to 5 years. It also recalled that some people in EMPOWER-Lung 3 continued to have treatment beyond 108 weeks because of dose pauses

(see section 3.9). So the committee expected that waning of treatment effect would start later than 2 years. The committee concluded that the company's modelling of a gradual waning of treatment effect from 3 to 5 years was appropriate.

Adverse event rates

3.12 In its model, the company included adverse events that were grade 3 and above and occurred in at least 5% of people in either treatment arm of EMPOWER-Lung 3 or the KEYNOTE trials. The rate of grade 3 and above adverse events for cemiplimab plus chemotherapy was sourced from EMPOWER-Lung 3. For pembrolizumab plus chemotherapy, the rates were sourced from KEYNOTE-189 and KEYNOTE-407 and weighted by histology as reported in EMPOWER-Lung 3. The EAG received clinical advice that the grade 3 and above adverse events included in the model would almost exclusively be caused by the chemotherapy regimens rather than the immunotherapies. The EAG noted that the company assumed the same chemotherapy regimens for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. So, the EAG preferred to apply the adverse event rates for pembrolizumab plus chemotherapy to both treatment arms. The committee noted that the choice of approach had a small impact on the cost-effectiveness results. It thought that it would be reasonable to source adverse event rates directly from the respective trials. It concluded that it preferred using the grade 3 and above adverse event rates from EMPOWER-Lung 3 and the KEYNOTE studies to model adverse event rates for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy, respectively.

Cost-effectiveness estimates

Acceptable ICER

3.13 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per

QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty about:

- the proportion of people with non-squamous NSCLC who would have cemiplimab without pemetrexed in clinical practice, and if EMPOWER-Lung 3 reflected this (see section 3.4)
- the comparative effectiveness of cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy (see sections 3.6 and 3.7)
- the use of a partitioned survival model (see section 3.8)
- the impact on overall survival of treatment after progression for people in the cemiplimab plus chemotherapy arm (see section 3.9).

The committee recalled that it had not seen the requested analysis using a Markov model structure (see section 3.8) or use of Kaplan–Meier data from EMPOWER-Lung 3 to calculate time on treatment for cemiplimab (see section 3.9) to explore these uncertainties. The committee concluded that an acceptable ICER would be around £20,000 per QALY gained.

Company and EAG cost-effectiveness estimates

3.14 Because of the confidential commercial arrangements for cemiplimab, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. The deterministic and probabilistic ICERs for cemiplimab plus chemotherapy in both the company's base case (using the NMA; see section 3.6) and alternative base case (using the MAIC; see section 3.7) were higher than the committee's acceptable ICER of around £20,000 per QALY gained (see section 3.13). The deterministic and probabilistic ICERs for

cemiplimab plus chemotherapy in the EAG's base case were considerably higher than the committee's acceptable ICER. The committee noted that although the company had implemented some of its preferred assumptions around stopping rules (see section 3.10), adverse events and treatment effect waning, and the EAG's base case included its preferred assumption about time on treatment for pembrolizumab, the committee was unable to define its preferred approach to modelling. This was because it had not seen the requested analysis using a Markov model structure to explore the uncertainty in the partitioned survival model structure (see section 3.7). Nor had it seen the requested analysis using Kaplan–Meier data from EMPOWER-Lung 3 to calculate time on treatment for cemiplimab (see section 3.9). The committee concluded that although there was no cost-effectiveness estimate that represented its preferred analysis, all of the cost-effectiveness estimates it had seen for the full target population were above the committee's acceptable ICER of around £20,000 per QALY gained. It was concerned that had the requested analysis been provided, these ICERs could have increased further.

Other factors

Equality

3.15 A clinical expert stated that for people with non-squamous NSCLC, pembrolizumab is given with pemetrexed plus platinum chemotherapy. In contrast, cemiplimab can be used without pemetrexed (given with paclitaxel plus platinum chemotherapy). The clinical expert considered this to be a potential equality issue because pemetrexed is associated with toxicity and may not be suitable for all people. The committee noted that the clinical expert had not highlighted any groups with protected characteristics, as per the Equality Act 2010, for whom pemetrexed would not be suitable. At the first meeting, the committee said it would welcome further comment during draft guidance consultation on any particular groups with a protected characteristic for whom pemetrexed would not be

suitable. No comments on this were received during consultation. The committee noted that it had not identified any particular groups with a protected characteristic for whom pemetrexed would not be suitable. The committee thought that its recommendation would not have a different impact on people protected by the equality legislation than on the wider population.

Uncaptured benefits and disadvantages

3.16 The company stated that cemiplimab plus chemotherapy allows greater flexibility to tailor chemotherapy regimens than pembrolizumab plus chemotherapy. Specifically, for people with non-squamous NSCLC, cemiplimab can be used without pemetrexed (given with paclitaxel plus platinum chemotherapy). It thought this was an advantage because pemetrexed is associated with toxicity and may not be suitable for all people. The company also stated that in EMPOWER-Lung 3, people were able to have a carboplatin area under the curve (AUC) 5 dose as an alternative to the AUC6 dose, which is associated with incremental toxicity. But the EAG noted that the AUC5 carboplatin dose is not routinely used for squamous NSCLC in the UK, because the NHS commissioning policy (Blueteq protocol) mandates that patients are 'fit' to have treatment with AUC6 carboplatin. In EMPOWER-Lung 3, most people with non-squamous NSCLC had chemotherapy with pemetrexed (see section 3.4). The committee thought that this may suggest that most people in clinical practice with non-squamous NSCLC having cemiplimab would have chemotherapy with pemetrexed. The committee also noted that for people with non-squamous NSCLC for whom pemetrexed is unsuitable, pembrolizumab plus chemotherapy would not be an appropriate comparator. But, it had not seen cost-effectiveness evidence in this population for any comparison other than cemiplimab plus chemotherapy compared with pembrolizumab plus chemotherapy. The company said that the subpopulation with non-squamous histology that cannot have pemetrexed could not be defined, so a cost-effectiveness analysis for this subpopulation was not possible, and the size of the subpopulation was

likely to be small. The EAG agreed that doing a cost-effectiveness analysis for this subpopulation would be challenging. The committee also noted that a potentially uncaptured disadvantage of cemiplimab plus chemotherapy was its more frequent, 3-weekly administration compared with the option of 6-weekly administration of pembrolizumab plus chemotherapy. The committee took into account the potential uncaptured benefits and disadvantages. It concluded that the added flexibility of chemotherapy regimens did not outweigh the committee's concerns that the cost-effectiveness estimates were not reliable enough for decision making and considerably above the committee's acceptable ICER (see section 3.14).

Conclusion

3.17 Because of the critical uncertainties in the economic modelling, and because it had not been presented with the analysis needed to define its preferences, the committee concluded that the available cost-effectiveness estimates were not suitable for decision making.

The committee noted that the cost-effectiveness estimates preferred by the company and the EAG were above the committee's acceptable ICER. The committee concluded that it had not seen evidence that cemiplimab with platinum-based chemotherapy represented a cost-effective use of NHS resources. So it should not be used for untreated NSCLC that:

- is locally advanced and not suitable for definitive chemoradiation, or metastatic
- has PD-L1 in 1% or more of the tumour cells and
- has no EGFR, ALK or ROS-1 aberrations.

Managed access

3.18 Having concluded that cemiplimab could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed access period. It noted that the

company had not provided a managed access proposal, and the committee had not seen evidence that cemiplimab with platinum-based chemotherapy had the plausible potential to be cost effective. So, a recommendation with managed access was not an option.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Amanda Adler, Raju Reddy

Vice chairs, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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Technical leads

Rachel Williams

Technical adviser

Louise Jafferally

Project manager

Ross Dent

Associate director

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