NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cemiplimab with platinum-based chemotherapy in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: February 2025

Note that this document is not NICE's final guidance on cemiplimab with platinum-based chemotherapy. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using cemiplimab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 26 March 2025
- Second evaluation committee meeting: To be confirmed.
- Details of the evaluation committee are given in section 4

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 definitive chemoradiation is unsuitable) or metastatic
- has PD-L1 in 1% or more of the tumour cells and
- has no EGFR, ALK or ROS-1 aberrations.

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

This is because there is not enough evidence to determine whether 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 an indirect comparison are uncertain.

There are concerns with the economic model. This is because of:

- the way the company structured its model
- uncertainty about how long people stay on treatment
- uncertainty about how long any benefits of cemiplimab last after treatment is stopped.

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) in combination 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.

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) compared with people who would have immunotherapy or chemotherapy alone. It explained that using 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, it 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. Some had cemiplimab with paclitaxel and carboplatin. 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 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 about 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 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

3.6 Because there was no direct evidence comparing cemiplimab plus chemotherapy with pembrolizumab plus chemotherapy, the company compared them indirectly and did network meta-analyses (NMAs). 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 HRs 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.

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 did not report data on overall survival adjusted for the effects of crossover. 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 viewed 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 acknowledged that the lack of access to patient-level data from the KEYNOTE trials prevented the company from doing a crossover-adjusted analysis. The company stated that overall survival data from the chemotherapy arm from EMPOWER-Lung 3 was similar to that from the KEYNOTE studies. So, it said that crossover in the KEYNOTE studies did not appear to have a large effect on overall survival. But 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. The committee noted that baseline characteristics specifically for people whose tumours express 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, and the differences increased uncertainty in the validity of the assumption of sufficient similarity across studies. The committee recognised that the KEYNOTE trials had longer post-progression follow up available than the EMPOWER-Lung 3 trial. So, the data on overall survival for pembrolizumab plus chemotherapy were 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. It concluded that the NMA results were highly uncertain, especially for overall survival.

Economic model

Model structure

3.7 The company provided a 3-state partitioned survival model, with a 30-year time horizon. It applied estimates of treatment effects from the 2-step NMA to the shape and scale parameters for 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 quality-adjusted life year (QALY) gain for cemiplimab plus chemotherapy predicted by the company's modelling primarily resulted from the NMA HR 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 between 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, the committee requested to see a Markov model structure based on progression-free survival data from the NMA, and with the assumption of equal mortality risk post-progression for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. The committee concluded that the partitioned survival model structure added uncertainty to the cost-effectiveness estimates and that it would like to see an alternative model structure explored.

Time to treatment discontinuation

3.8 The EMPOWER-Lung 3 protocol allowed people to continue having cemiplimab after disease progression. The company stated that in EMPOWER-Lung 3, most people did not have access to post-progression second-line immunotherapy treatments, which likely led to staying on cemiplimab beyond progression 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 3.9). 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 that it preferred the ratio method to calculate time on treatment for pembrolizumab (until the stopping rule was applied; see section 3.9) 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. This should also include treatment costs for people who continued treatment beyond 108 weeks (see section 3.9).

Stopping rule

3.9 The company included a 2-year stopping rule for cemiplimab in the model. 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. This was because at approximately 27 months, 42 people were still having cemiplimab. The committee requested that the

implementation of the stopping rule for cemiplimab in the model should reflect EMPOWER-Lung 3. For pembrolizumab, the committee requested that the company update the implementation of the stopping rule in the model, to reflect NHS practice of 35, 3-weekly cycles.

Waning of treatment effect after stopping treatment

3.10 For both cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy, the company assumed that the treatments continued to be effective beyond 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 viewed 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 committee noted that 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. The committee concluded that it preferred a gradual approach to treatment waning, rather than an immediate waning of treatment effect. The committee 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.

Adverse event rates

3.11 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

Company and EAG cost-effectiveness estimates

3.12 Because of the confidential commercial arrangements for the prices of 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 incremental cost-effectiveness ratios (ICERs) for cemiplimab plus chemotherapy in the company's base case were higher than the range normally considered an acceptable use of NHS resources. The deterministic and probabilistic ICERs for cemiplimab plus chemotherapy in the EAG's base case were considerably higher than the range normally considered an acceptable use of NHS resources.

Acceptable ICER

3.13 NICE's manual on health technology evaluations notes that, above a most plausible 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 section 3.6)
- the use of a partitioned survival model (see section 3.7)
- the impact on overall survival of treatment beyond progression for people in the cemiplimab plus chemotherapy arm (see section 3.8)

- the impact on progression-free survival and overall survival of continued treatment beyond 108 weeks for people in the cemiplimab plus chemotherapy arm (see section 3.8)
- the implementation of the stopping rules for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy (see section 3.9)
- the long-term treatment effect of cemiplimab plus chemotherapy relative to pembrolizumab plus chemotherapy after stopping treatment (see section 3.10).

The committee concluded that an acceptable ICER would be around £20,000 per QALY.

The committee's preferences

3.14 For the cost-effectiveness analysis, the committee preferred:

- using a ratio between time on treatment and progression-free survival to calculate time on treatment for pembrolizumab (see section 3.8)
- using Kaplan–Meier data from EMPOWER-Lung 3, either directly or using the best fitting parametric survival curve fitted to that data, as per the NICE technical support document 14 to calculate time on treatment for cemiplimab. This should also include treatment costs for people who continued treatment beyond 108 weeks (see section 3.8)
- the stopping rule for pembrolizumab to be implemented such that pembrolizumab is stopped after 35, 3-weekly cycles (see section 3.9)
- assuming a gradual waning of treatment effect for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy (see section 3.10)
- 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 (see section 3.11).

The committee's requests for additional analyses

3.15 The committee could not determine the most plausible ICER without further analyses. The committee requested the following:

- a Markov model based on progression-free survival data from the NMA, with the assumption of equal mortality risk post-progression for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy (see section 3.7)
- calculating time on treatment for cemiplimab using Kaplan–Meier time-on-treatment data from EMPOWER-Lung 3, either directly or using the best fitting parametric survival model fitted to that data, as per NICE technical support document 14. This should also include people who continued treatment beyond 108 weeks (see section 3.8)
- implementing the stopping rule for pembrolizumab such that pembrolizumab is stopped after 35, 3-weekly cycles (see section 3.9)
- implementing the stopping rule for cemiplimab such that it reflects EMPOWER-Lung 3 (see section 3.9)
- further justification from the company to support a 5-year waning time point, including analysis of 5-year data from KEYNOTE-189 and KEYNOTE-407. 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 (see section 3.10)
- further evidence to support a 5-year waning time point based on data specifically for cemiplimab plus chemotherapy (see section 3.10).

Other factors

Equality

3.16 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. The committee would welcome further comment during draft guidance consultation on any particular groups with a protected characteristic for whom pemetrexed would not be suitable.

Uncaptured benefits

3.17 The company stated that cemiplimab plus chemotherapy allows greater flexibility to tailor chemotherapy regimens compared with 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 people with squamous NSCLC in the UK, because the NHS commissioning policy (Blueteq protocol) mandates that patients are 'fit' to have treatment with AUC6 carboplatin. The committee noted that in EMPOWER-Lung 3, most people with non-squamous NSCLC had a chemotherapy regimen with pemetrexed. It thought that this may suggest that most people in clinical practice with non-squamous NSCLC having cemiplimab would have a chemotherapy regimen with pemetrexed. The distribution of chemotherapy regimens is considered confidential by the company and cannot be reported here. 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 committee also noted that a potentially uncaptured disadvantage of cemiplimab plus

chemotherapy was its more frequent 3-weekly administration compared with the option for 6-weekly administration of pembrolizumab plus chemotherapy. The committee concluded it would take into account any potential uncaptured benefits and disadvantages when it was presented with new modelling. If further concluded that the added flexibility of chemotherapy regimens did not outweigh the committee's concerns about the cost-effectiveness estimates and the degree of uncertainty around the ICER.

Conclusion

3.18 The committee agreed that further information was needed before it could decide on all of its preferred modelling assumptions and understand the full impact of the uncertainties. So, it was unable to establish that cemiplimab plus chemotherapy was a cost-effective use of NHS resources. It concluded that cemiplimab with platinum-based chemotherapy should not be used for untreated locally advanced (when definitive chemoradiation is unsuitable) or metastatic NSCLC that has PD-L1 in 1% or more of the tumour cells and has no EGFR, ALK or ROS-1 aberrations.

Managed access

3.19 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. The committee noted that the company had not provided a managed access proposal and there was not yet a plausible cost-effectiveness estimate. 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

Vice chair, 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.

Dilan Savani

Technical lead

Rachel Williams

Technical adviser

Louise Jafferally

Project manager

Ross Dent

Associate director

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