NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Pembrolizumab for adjuvant treatment of resected 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 pembrolizumab 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?

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Note that this document is not NICE's final guidance on this technology. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using pembrolizumab in the NHS in England.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: 19 September 2024
- Second evaluation committee meeting: 3 October 2024
- Details of the evaluation committee are given in section 4

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1 Recommendations

1.1 Pembrolizumab is not recommended, within its marketing authorisation, for adjuvant treatment of non-small-cell lung cancer (NSCLC) that is at high risk of recurrence after complete resection and platinum-based chemotherapy in adults.

1.2 This recommendation is not intended to affect treatment with pembrolizumab 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.

Why the committee made these recommendations

The company positioned pembrolizumab for adjuvant treatment of NSCLC that is at high risk of recurrence after complete resection and platinum-based chemotherapy in adults whose tumours have the PD-L1 biomarker expression on less than 50% of their tumour cells. This is narrower than the population it is licensed for. Usual treatment for people in this narrower population is active monitoring.

Clinical trial evidence shows that people with NSCLC who have pembrolizumab have longer before their cancer gets worse and live longer compared with people who have placebo. But how well pembrolizumab works in the narrower population, compared with the population it is licensed for, is uncertain.

Because of uncertainty in the clinical-effectiveness evidence for the narrower population, the assumptions used to estimate cost effectiveness are also uncertain. So it is not possible to reach a reliable cost-effectiveness estimate and pembrolizumab is not recommended.

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2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme) is indicated for 'the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £2,630 per 100-mg vial (excluding VAT; BNF online accessed August 2024).

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

3 Committee discussion

The evaluation committee considered evidence submitted by Merck Sharp & Dohme, 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

Treatment options

3.1 Non-small-cell lung cancer (NSCLC) is staged from 1A to 4B according to the size and extent of the tumour, location of involved lymph nodes and the presence of distant metastases. This is based on the American Joint Committee on Cancer eighth edition staging system. Resectable NSCLC

is usually considered to be early to locally advanced cancer (stage 1A to 3B). Standard care for people with resectable NSCLC is complete surgical resection. Surgery can cure the cancer, but recurrence is common and can either be local-regional (within the lungs and nearby lymph nodes) or distant metastatic (other part of the body). Before surgery, people have the option of neoadjuvant nivolumab with chemotherapy or active monitoring. After complete surgical resection, people have the following options:

- active monitoring
- osimertinib, which is available through the Cancer Drugs Fund (CDF) for people with epidermal growth factor receptor (EGFR) mutation-positive NSCLC (see NICE's technology appraisal guidance on osimertinib)
- adjuvant chemotherapy
- adjuvant chemotherapy followed by maintenance treatment with atezolizumab, which is available through the CDF for people with NSCLC whose tumours express the biomarker PD-L1 on 50% or more of their tumour cells (from now on referred to as PD-L1 tumour proportion score [TPS] 50% or more; see NICE's technology appraisal guidance on atezolizumab).

Clinical expert submissions stated that the aim of adjuvant treatment is to reduce the risk of recurrence after surgery for people with potentially curable NSCLC. The committee considered data presented that showed that 41% of people with stage 1 to 3 lung cancer with complete resection develop recurrence within 23 months. The patient organisation submission reported that recurrence of NSCLC after surgery usually means that further curative treatment is unlikely. It explained that the only way to tell if surgery has been curative is to wait, and this results in continual anxiety for people with lung cancer and their families and carers. The company proposed adjuvant pembrolizumab for NSCLC in adults with a high risk of recurrence after

complete resection and platinum-based adjuvant chemotherapy, but only if their tumours have a PD-L1 TPS less than 50%. The committee understood that there are no other immunotherapy treatment options available at this point in the treatment pathway. The patient organisation submission stated that there is an ongoing need to develop additional treatments that would reduce the risk of recurrence. The committee concluded that there was an unmet need for a treatment that reduces the risk of recurrence after complete resection.

Comparators

3.2 The company compared adjuvant pembrolizumab with active monitoring. The final scope for this evaluation also included:

- platinum doublet chemotherapy
- durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant; subject to NICE appraisal)
- adjuvant osimertinib (subject to NICE appraisal) and
- adjuvant atezolizumab (subject to NICE appraisal).

The company explained that people eligible for adjuvant pembrolizumab would have had adjuvant chemotherapy and so platinum doublet chemotherapy was not a relevant comparator. It also added that because of its proposed population of people with a PD-L1 TPS less than 50% (see section 3.1), atezolizumab, durvalumab and osimertinib were not considered appropriate comparators. This is because they are suitable for a different population, and are not considered standard care. So, it considered there was no alternative to pembrolizumab for this population and the relevant comparator is active monitoring. The committee agreed that adjuvant pembrolizumab would be used after platinum doublet chemotherapy, as in its marketing authorisation, and so platinum doublet chemotherapy is not an appropriate comparator. Durvalumab would be suitable for a different population after neoadjuvant treatment and osimertinib and atezolizumab are not routinely commissioned because

they are only available within the CDF. Therefore, the committee agreed that active monitoring was the relevant comparator to pembrolizumab in this proposed population.

Clinical effectiveness

Clinical trial evidence

3.3 The clinical evidence for adjuvant pembrolizumab came from the KEYNOTE-091 phase 3 randomised controlled trial. KEYNOTE-091 compared adjuvant pembrolizumab (200 mg every 3 weeks for 1 year) with placebo in adults with stage 1B (tumour size equal to or more than 4 cm), 2 or 3A NSCLC after complete surgical resection and with or without adjuvant chemotherapy. The primary outcome measure was disease-free survival (DFS). A key secondary outcome measure was overall survival (OS). The trial stratification factors included the use of previous adjuvant chemotherapy and PD-L1 status (with TPS less than 1%; between 1% and 49%; and more than 50%). The population in the marketing authorisation is adults who had previous adjuvant chemotherapy (see section 2.1). In line with its proposed population, the company provided post hoc subgroup results from a subpopulation of adults who had previous adjuvant chemotherapy and whose tumours had a PD-L1 TPS less than 50%. Results from an interim analysis with a data cutoff date of January 2023 were reported for 3 populations:

- overall trial population (pembrolizumab n=590; placebo n=587)
- previous adjuvant chemotherapy population (licensed population; pembrolizumab n=506; placebo n=504)
- PD-L1 TPS less than 50% population (proposed population; pembrolizumab n=363; placebo n=363).

Adjuvant pembrolizumab was associated with a statistically significantly improvement in DFS compared with placebo for all populations, but the greatest benefit was seen in the PD-L1 TPS less than 50% population:

- overall trial population: hazard ratio 0.81 (95% confidence interval [CI]: 0.68 to 0.96)
- previous adjuvant chemotherapy population: hazard ratio 0.76 (95% CI: 0.64 to 0.91)
- PD-L1 TPS less than 50% population: hazard ratio 0.72 (95% CI: 0.58 to 0.89).

Adjuvant pembrolizumab was also associated with improved OS compared with placebo for all populations, and the greatest benefit was again seen in the PD-L1 TPS less than 50% population:

- overall trial population: hazard ratio 0.87 (95% CI: 0.69 to 1.10)
- previous adjuvant chemotherapy population: hazard ratio 0.79 (95% CI: 0.62 to 1.01)
- PD-L1 TPS less than 50% population: hazard ratio 0.73 (95% CI: 0.55 to 0.97).

PD-L1 TPS less than 50% subgroup data

3.4 The company proposed pembrolizumab as an adjuvant treatment for adults with NSCLC after complete surgical resection and adjuvant chemotherapy and whose tumours have a PD-L1 TPS less than 50% (see section 3.1). This was a narrower population than in the NICE final scope and the marketing authorisation (see section 2.1). The company explained that this positioning of pembrolizumab is consistent with the clinical trial results, in which this subpopulation had the greatest clinical benefit from adjuvant pembrolizumab compared with placebo (see section 3.3). But, this subgroup was not prespecified in the KEYNOTE-091 trial, so the results were from a post hoc analysis. The company also noted that this subpopulation has a large unmet need and could benefit most from an additional adjuvant option. The committee recalled that there are currently no other adjuvant treatment options for people whose tumours have a PD-L1 TPS less than 50% (see section 3.1). The EAG was concerned that the decision to focus on this subgroup was driven by the data rather

than biological plausibility. Also that the data was from a post hoc analysis and so could be at risk of bias and type 1 error. This means that the data could potentially overestimate the effectiveness of pembrolizumab compared with placebo in this subpopulation. It explained that the smaller sample size of this post hoc subgroup, which was a subpopulation of the prespecified population (see section 3.3), reduced the power of the analyses. This prevents reliable conclusions being drawn and increases the risk that the results are down to chance. The committee considered the clinical-effectiveness results. It questioned why the full licensed population was not the focus of this evaluation, given that adjuvant pembrolizumab was also more effective than placebo in this broader population. The company stated that people whose tumours have a PD-L1 TPS of 50% or more were excluded from the proposed population because there is uncertainty about whether pembrolizumab is more clinically and cost effective compared with atezolizumab. It explained that clinical feedback suggested that pembrolizumab is not expected to become the preferred treatment option over atezolizumab. Clinical expert submissions disagreed, explaining that they expect more people to have adjuvant pembrolizumab. This is because using pembrolizumab as an alternative to atezolizumab for people with a PD-L1 TPS of 50% or more could give people the option of a treatment that is given less frequently, every 6 weeks rather than every 3 to 4 weeks. The committee was aware that atezolizumab was recommended through the CDF and so is not considered established practice in the NHS (see section 3.2). It understood that after a period of managed access, NICE will review the technology to decide if it can be recommended for routine commissioning.

The committee considered that there is an unmet need for people with a PD-L1 TPS of more or less than 50%, because there are currently no established treatments. It also noted that the KEYNOTE-091 results unexpectedly showed that adjuvant pembrolizumab was less effective in the PD-L1 TPS 50% or more subgroup than the PD-L1 TPS less than

50% subgroup. The company's UK Clinical Advisory Board supported this, noting that the KEYNOTE-091 results for the PD-L1 TPS 50% or more subgroup contradicted clinical expectations. This is because there is established evidence that PD-1 inhibitors, such as pembrolizumab, typically have a greater efficacy in the PD-L1 TPS 50% or more subgroup. This was supported by clinical experts who explained that the KEYNOTE-091 trial was designed with this clinical expectation. This was why the PD-L1 TPS 50% or more subgroup was a stratification factor in the trial and the PD-L1 TPS less than 50% subgroup was not predefined. The EAG's clinical experts supported this and noted that the mechanism underpinning greater clinical benefits in the PD-L1 TPS less than 50% subgroup is not yet understood. The company suggested that the reason for these results was because the trial placebo arm in the PD-L1 TPS 50% or more subgroup performed better than expected. But the EAG highlighted that the company had not provided evidence to support this claim and the placebo arm could have instead underperformed in the PD-L1 TPS less than 50% subgroup. The committee noted that the company's proposed positioning of adjuvant pembrolizumab was in a narrower population than that in the NICE final scope and that the results of KEYNOTE-091 could not be clinically explained so could be due to chance. It was aware that the NICE health technology evaluations manual section on analysis of data for patient subgroups states that subgroups should be based on an expectation of differential clinical or cost effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. The committee considered that the company's decision to focus on the PD-L1 TPS less than 50% subgroup was not driven by biological plausibility. Instead, it had been driven by the unexpected clinical findings and the potential impact this had on the cost effectiveness of pembrolizumab. Given that the company and the clinical experts could not explain the results from this post hoc subgroup, the clinical and cost effectiveness of adjuvant pembrolizumab remains highly uncertain. The committee was not presented with cost-

effectiveness analyses in the licensed population. It also rejected the justification for restricting pembrolizumab to the PD-L1 TPS less than 50% subgroup when there are no routinely commissioned treatments available in the PD-L1 TPS 50% or more subgroup. It did not consider that the results from the PD-L1 TPS less than 50% subgroup were convincing, given their post hoc nature. It considered that the findings could be a result of chance. The committee concluded that it would like to see an analysis using the full licensed population, in addition to any subgroups which are based on known biologically plausible mechanisms, social characteristics or other clearly justified factors.

Baseline age

3.5 The mean age of the KEYNOTE-091 overall trial population was 64.3 years, and this was also the starting age in the economic model. The EAG's clinical experts highlighted that this was younger than seen in NHS clinical practice. So the EAG was concerned about the generalisability of the KEYNOTE-091 trial age to clinical practice and the potential impact of this on the cost-effectiveness results. The EAG's clinical experts also noted that fewer people are likely to be cured in an older population (see section 3.7). The EAG was also concerned that age may be a treatment effect modifier. The company highlighted that the treatment effect of pembrolizumab did not differ across age groups in the PD-L1 TPS less than 50% DFS subgroup analysis. Clinical experts supported this, explaining that they had not seen age appear as an independent prognostic factor in lung cancer. In its base case, the EAG's starting age was 68 years based on registry data from people with NSCLC who had surgery in England in 2012. The company stated that people having adjuvant pembrolizumab must be fit enough to have surgery and to complete adjuvant chemotherapy, so would likely be younger than the average person diagnosed with NSCLC. This was supported by clinical experts who explained that the NHS targeted lung health check programme would likely result in more cases being diagnosed at earlier stages and in younger people. They considered that it was reasonable to

expect the average age of people with NSCLC to decrease over time. The committee noted the evidence and considered that it was plausible that the mean age would change with time. But it was aware that decision making should be based on data from current clinical practice. The NHS CDF clinical lead informed committee that the mean age of people having atezolizumab through the CDF in NHS practice (see the NICE technology appraisal guidance on atezolizumab) is 67 years. They expected this to be generalisable to the proposed population in this appraisal. The committee considered that the age of people in KEYNOTE-091 may reflect a younger and fitter population than in NHS clinical practice. As a result, the effectiveness data from the trial used throughout the model may also reflect such a population. This added to the uncertainty around the effectiveness of adjuvant pembrolizumab. The committee concluded that KEYNOTE-091 had a lower mean age than the potential population in current NHS practice, and that 67 years was the most appropriate age to be modelled.

Economic model

Company's modelling approach

3.6 The company developed a Markov state-transition model with 4 health states to model the cost effectiveness of adjuvant pembrolizumab compared with active monitoring. The health states were DFS, local-regional recurrence (LR), distant metastases (DM), and death. People enter the model in the DFS health state and move to the LR or DM health states, depending on the type of recurrence event they have. From LR, people could move to DM, and people could move to the death state from any other health state. Pembrolizumab was modelled to increase the probability of a cure in the long term, rather than just delaying recurrence. The model included a cure assumption, which meant that a proportion of people in the DF health state at a given time point would be considered cured (see section 3.7). This meant people who had pembrolizumab remained in the DF health state longer than people who had active

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monitoring. So fewer people experienced transitions to the recurrence health states, LR and DM. This separation in DFS between treatment arms was expected to continue (see section 3.8) and translate roughly into the same improvements in OS. This model structure implied that DFS was a surrogate outcome for OS. In the absence of robust KEYNOTE-091 data, external data was used to model recurrence transition probabilities from LR and DM. To better align the modelled OS with the observed OS from the KEYNOTE-091 trial, the company applied a multiplier (see section 3.10). The biggest driver of the modelled benefits of pembrolizumab compared with active monitoring was the improvement in OS. The committee noted that there were some uncertainties because the lifetime survival extrapolations were reliant on DFS and there was limited OS data available. It considered the structure of the model to be acceptable for decision making.

Assumptions around cure

3.7 The company model contained a cure assumption. It assumed that in the DFS health state, the proportion of people cured would rise from 0% at 5 years to 95% at 7 years. People considered cured were assumed to have no risk of transitions out of the DFS state to LR or DM states. The EAG highlighted that the 95% reduction in risk of recurrence originates from the NICE technology appraisal guidance on pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. It was used in addition to a 5-year cure point so that the model's long-term recurrence rate aligned with the breast cancer literature. The EAG explained that a 95% cure rate was specific to that appraisal and has not been clinically validated. It highlighted that there is substantial uncertainty in what the exact cure point and cure rate is for early NSCLC. The company responded that, in its base case, the proportion of modelled ultra-late recurrences was in line with the NSCLC literature when using this 95% rate, which suggests that it is appropriate. The EAG noted that, when used in its base case, the ultra-late recurrence rate was lower than the NSCLC literature and that a 75% cure rate would be needed to align with

the literature. The committee considered that the modelled proportion of ultra-late recurrences should align with the NSCLC literature. People who remain in the DFS health state in the model were assumed to have age- and sex-matched general population mortality. The EAG's clinical experts advised that even people who remain in the DFS health state will have a mortality rate 50% to 60% higher than the general population. They explained this is caused by lasting damage to the lungs from cancer and surgery. To represent the higher risk of mortality in the cured fraction, the EAG thought a standardised mortality ratio of 1.5 should be applied to general population mortality. The company noted that all-cause mortality at year 15 in the model is already approximately 1.5 times that of the general population, which the EAG accepted. The committee considered that the modelling of cure was broadly appropriate in the company's base case. But it noted that the all-cause mortality for people remaining in the DFS health state should align with the clinical opinion. It concluded that the appropriateness of applying a standardised mortality ratio and using a 95% cure rate should be reassessed in any new analyses presented (see section 3.4).

Treatment effect waning

3.8 The company did not apply any treatment effect waning in the model. This meant that the benefits of adjuvant pembrolizumab were assumed to be sustained throughout the lifetime horizon. It stated that time in the DFS health state was only determined by the cure assumption (see section 3.7), the background mortality rates and the parametric models selected (see section 3.9). The company explained that pembrolizumab is a PD-1 inhibitor that blocks the interaction between PD-1 receptors and PD-L1 proteins, helping immune cells to attack cancer cells. It explained that this mechanism of action (see the summary of product characteristics for pembrolizumab) supports a sustained treatment effect. It said that this has been observed in both the KEYNOTE-091 trial and in long-term data from other pembrolizumab indications. The EAG disagreed with the company, stating that there was significant evidence of treatment effect

waning in the pembrolizumab arm. It noted that in the observed DFS data for the PD-L1 TPS less than 50% subgroup in KEYNOTE-091, the treatment benefit of pembrolizumab compared with placebo declines at every timepoint from 18 months. The company stated that the difference in observed DFS between pembrolizumab and placebo in KEYNOTE-091 remains relatively consistent until year 4. After year 4 the DFS difference meaningfully narrows, but at this point around two-thirds of people in the trial are censored and there are a very small number of events (n=19). So the company said that a conclusion of treatment waning based on very limited data would be inappropriate. The EAG acknowledged that the data available at 5 years is limited. But it noted that there is no other information to inform modelling, and the company still considered there to be enough data at these timepoints to make extrapolations assumptions (see section 3.9). The clinical experts explained that it is biologically plausible that immunotherapies could increase the proportion of people cured and that they would expect the DFS separation to continue between pembrolizumab and active monitoring. They added that this was supported by their experience in clinical practice, where many people had survived after having immunotherapy. But, they noted that there would be some people for whom the treatment effect would stop after finishing treatment. The committee acknowledged that the observed DFS curves tended together towards the end of the Kaplan–Meier curves. But it recognised that this was based on few numbers of people left at risk so was not a reliable assessment of treatment waning. It considered that a waning of the benefits of adjuvant pembrolizumab was clinically plausible, but that this had not been fully explored within the modelling. Treatment effect waning could be captured in a model either explicitly, for example, by assuming the hazard ratios increase over time, or implicitly by accounting for waning in the survival estimates through selected parametric survival models. The committee concluded that it would like to see treatment waning explored within the new analyses in response to the draft guidance.

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DFS modelling

3.9 The transition rates of people moving from the DFS health state were determined using data for the PD-L1 TPS less than 50% subgroup in KEYNOTE-091. The company fitted individual parametric models to each of the 3 transitions from DFS (DFS to LR, DFS to DM and DFS to death) and to each treatment arm. The company determined the statistical and visual fit of the parametric models for each transition and treatment arm in combination. It also took into account the NICE Decision Support Unit technical support document 14 (TSD14). It states that if the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type. The company applied the same parametric model to both pembrolizumab and active monitoring. This was a log-normal model for the transitions from DFS to LR and DFS to DM, and the exponential model for the transition from DFS to death. The EAG noted that the company's model selection did not account for the treatment effect waning in the pembrolizumab arm of the KEYNOTE-091 trial (see section 3.8). To capture this, the EAG chose to select different parametric models for the pembrolizumab and active monitoring arm. TSD14 states that it may be appropriate to fit separate parametric models to individual treatment arms, but to do so would require substantial justification as different models allow very different shaped distributions. The EAG believed that because waning was visible within the observed DFS data, selecting different parametric curves for each treatment arm may be a reasonable way to account for this. For the transition from DFS to LR, the EAG modelled an exponential curve for pembrolizumab and a generalised gamma curve for the active monitoring arm. For the transition from DFS to DM, a log-normal curve was selected for the pembrolizumab arm and a Gompertz model for active monitoring. Like the company, the EAG used the exponential curve to model the transition from DFS to death in both treatment arms.

The company responded that stronger evidence is needed to use different models for each treatment arm. It highlighted that modelling

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pembrolizumab to only delay recurrence and have no curative advantage is contrary to clinical expectation (see section 3.7). The company stated that using an exponential curve, which assumes a constant risk of hazard, to model the transition from DFS to LR in the pembrolizumab arm is likely to be inappropriate. This is because the risk of recurrence decreases over time as more people are cured. It also noted that using a Gompertz curve, which assumes no risk of recurrence soon after follow up, is likely inappropriate to model the DFS to DM transition in the placebo arm. This is because there is well-established evidence that shows that there are ultra-late recurrences in early NSCLC. Applying these curves to only one of the treatment arms was also challenged by the company. The EAG responded that these were the best fitting curves to the observed data and the cure period. The company suggested alternative DFS curves that it believed had good visual and statistical fit, clinically plausible projections and followed the TSD14 guidance. This was the generalised gamma curve to model the transition DFS to LR and the log-normal curve to model the DFS to DM transition. The committee considered the 3 different DFS curve selections presented. It noted that the EAG modelled DFS rates were the closest to the observed DFS from KEYNOTE-091 in both the treatment arms. But it did not think there was enough justification to deviate from the TSD14 guidance of using the same parametric function in both treatment arms. The committee considered the company's proposed curves but noted that not enough evidence had been presented to select any. It concluded that it would like to see DFS modelled using the full licence population and the PD-L1 TPS less than 50% subgroup (see section 3.4). This should ensure that the post-cure rate of recurrence aligns with NSCLC literature (see section 3.7) and treatment waning is captured appropriately (see section 3.8).

Recurrence transitions

3.10 The transition rates for people who have disease recurrence were estimated based on external data. This is because appropriate data from the KEYNOTE-091 trial to inform the transitions was unavailable. To

estimate the recurrence transition from the LR and DM health states, NSCLC literature and data from trials of subsequent treatments was used, respectively. Recurrence transitions were modelled in both treatment arms with an exponential curve. The company explained that using external data to model the pembrolizumab arm resulted in significantly different OS estimates compared with the KEYNOTE-091 results and real-world data. In order to match the OS curves to the observed OS data, the company applied a single multiplier to all recurrence transitions in both arms. The EAG highlighted that calibrating the modelled OS to the observed OS in this way relied upon combining multiple assumptions. This led to significant uncertainty in the modelled transition rates. Without access to the data, it could not validate whether the exponential curves were a reasonable fit. The EAG also considered it unlikely that a single modifier and the same parametric distribution would be appropriate to use across each transition and for both treatment arms, particularly because it believed there was evidence of treatment effect waning (see section 3.8). The EAG explained that within the time constraints, no alternative approach had been presented, which made the cost-effectiveness estimates uncertain and the direction of the bias of this calibration approach unclear. To resolve this, it noted that using a partitioned survival model structure or adapting the model structure to allow for time-dependent transitions in people with recurrence would allow different modelling methods to be tested. Also it said that further investigation of the KEYNOTE-091 individual patient-level data would be useful to help to inform transition rates. The committee noted that the OS data was not very mature (pembrolizumab: 23%; placebo: 30% of OS events occurred), which meant that lifetime extrapolation of this data was very uncertain. The clinical experts supported this, explaining that there is not enough OS data for them to estimate long-term survival. The committee considered the large amount of uncertainty in the modelled transition rates and was not satisfied with the OS calibration that had been applied. The committee concluded that it would like to see additional analyses that explored these

uncertainties with transitions at later lines. For example, analysis that validates the OS modelling assumptions, such as providing visual fits of post-calibration extrapolations over observed OS and DFS data, for intermediate transition. Also, an exploration of the uncertainties in the model structure. For example, using mixture cure models, making post-recurrence extrapolation cures time-dependent, and applying a modifiable risk ratio to the transition rates of LR to death and DM to death, to match modelled OS.

Severity

3.11 The company did not make a case to apply the severity modifier. NICE's methods on conditions with a high degree of severity did not apply.

Cost-effectiveness estimate

Company and EAG cost-effectiveness estimates

3.12 The company and EAG had different interpretations of the KEYNOTE-091 clinical trial data (see section 3.3). The company assumed that the pembrolizumab benefit increases the proportion of people cured, but the EAG assumed that the pembrolizumab benefits represented a delay in recurrence (see section 3.7). The company also assumed that the benefits of pembrolizumab were sustained across the time horizon, whereas the EAG thought these would wane over time (see section 3.8). Their base cases differed by 2 key inputs, the model starting age (see section 3.5) and the curves used to model transitions from the DFS health state (see section 3.9). The biggest driver of cost effectiveness was how DFS was modelled. The company's base case was below £30,000 per quality-adjusted life year (QALY) gained and the EAG's base case was above £30,000 per QALY gained.

Committee's preferred cost-effectiveness estimate

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 considered that the most appropriate baseline age to model was 67 years, in line with NHS clinical practice data (see section 3.5). It noted the high levels of uncertainty in the model, which arose from:

- the data informing the effectiveness of pembrolizumab in the PD-L1 TPS less than 50% subgroup, which is from a post hoc subgroup for which the relative treatment effect could not be clinically explained (see section 3.4)
- the way in which the assumption of cure was modelled and what mortality cured people would have (see section 3.7)
- the limited DFS evidence after 4 years, which meant that the duration of treatment effect and the most appropriate modelling of DFS is unknown (see sections 3.8 and 3.9)
- the recurrence transition rates and modelling of OS, which is based on multiple combined assumptions (see section 3.10).

The committee cannot establish its preferred cost-effectiveness estimates and threshold until it has been presented with an analysis using the full licence population, in addition to any subgroups which are based on a known biologically plausible mechanisms, social characteristics or other clearly justified factors (see section 3.4). It wanted these analyses to:

- assess the appropriateness of a 95% reduction in risk of recurrence
- model a post cure rate of recurrence that is aligned with external NSCLC literature
- ensure the mortality rate of those who remain in the DFS health state to be 50% to 60% higher than general population mortality

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- further explore modelling treatment waning within its DFS curve selection
- validate the modelling of OS (for example, providing visual fits of post-calibration extrapolations over observed OS and DFS data)
- explore the uncertainties in the model structure (for example, using mixture cure models, making post-recurrence extrapolation cures time-dependent, and applying a modifiable risk ratio to the transition rates of LR to death and DM to death, to match modelled OS).

Managed access

3.14 Having concluded that pembrolizumab could not be recommended for routine use, the committee then considered if it could be recommended with managed access. The committee noted that a managed access proposal had not been provided by the company and that there was not yet a plausible cost-effective estimate, so a recommendation with managed access was not an option.

Other factors

Equality

3.15 The committee did not identify any equality issues.

Conclusion

Recommendation

3.16 The committee had concerns about the company's positioning of pembrolizumab as an adjuvant treatment for NSCLC in adults with high risk of recurrence after complete resection and platinum-based chemotherapy and whose tumours have a PD-L1 TPS less than 50%. This was because the large clinical benefits associated with this population were unexpected, based on a post hoc subgroup and could not be clinically explained. The committee considered that the clinical and cost-effectiveness evidence for the full licence population, in addition to this subgroup, was needed before decisions were made about the most

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appropriate modelling assumptions. So it did not recommend pembrolizumab as an adjuvant treatment of NSCLC in adults with high risk of recurrence after complete resection and platinum-based chemotherapy.

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

Raju Reddy

Vice Chair, technology appraisal committee D evaluation committee

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.

Cara Gibbons

Technical lead

Adam Brooke

Technical adviser

Celia Mayers

Project manager

Jasdeep Hayre

Associate director

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