NICE National Institute for Health and Care Excellence

NICE guidance

Pembrolizumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Pembrolizumab is recommended, within its marketing authorisation, as an option for neoadjuvant treatment with platinum-based chemotherapy, then continued alone as adjuvant treatment, for resectable non-small-cell lung cancer (NSCLC) with a high risk of recurrence in adults. Pembrolizumab is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Usual treatment for resectable NSCLC with a high risk of recurrence in adults is nivolumab with chemotherapy, then surgery. A resectable tumour is one that can be removed surgically.

Clinical trial evidence shows that, compared with placebo, pembrolizumab with platinum-based chemotherapy before surgery (neoadjuvant) then pembrolizumab alone after surgery (adjuvant) decreases the likelihood of:

- an event that would stop people having surgery (for example, the cancer getting worse), and
- the cancer coming back after surgery.

It also shows that people having pembrolizumab live longer than those having placebo.

Pembrolizumab has not been directly compared in a clinical trial with neoadjuvant nivolumab with chemotherapy. An indirect comparison suggests that pembrolizumab may reduce the likelihood of the cancer getting worse or coming back after surgery compared with neoadjuvant nivolumab, but this is uncertain.

The cost-effectiveness estimates for pembrolizumab are within the range that NICE considers an acceptable use of NHS resources. So, pembrolizumab is recommended.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp and Dohme) 'in combination with platinum-containing chemotherapy, as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small-cell lung carcinoma at high risk of recurrence in adults'.

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. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Merck Sharp and 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

Current treatment options

3.1 Standard care for resectable non-small-cell lung cancer (NSCLC) is neoadjuvant nivolumab with chemotherapy and surgical resection (from now, neoadjuvant nivolumab). Other treatment options include neoadjuvant chemoradiotherapy, and adjuvant chemotherapy with or without maintenance atezolizumab treatment through the Cancer Drugs Fund (CDF). Resectable NSCLC is usually early stage or locally advanced cancer, not including stage 3C. Surgery can cure the cancer, but recurrence is common and can either be locoregional (within the lungs and nearby lymph nodes) or distant metastatic (other parts of the body). 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 the condition and their families and carers. The patient organisation and clinical experts stated that there is an ongoing need to explore additional treatment options that would reduce the risk of recurrence. The committee noted that reducing the likelihood of recurrence was important to people with the condition and healthcare professionals. It concluded that new treatments that could achieve this would be welcomed.

Treatment pathway and treatment choice

3.2 A clinical expert explained that surgery has a big impact on people's physical and mental health and many people who have surgery are not well enough to have adjuvant treatment. They noted that, in their experience, 30% to 40% of people

might choose not to have adjuvant treatment. The clinical expert explained that if neoadjuvant treatment is used to reduce tumour size before surgery, people are more likely to be well enough to continue with adjuvant treatment. They stated that there may be some people who are eligible for neoadjuvant nivolumab but do not have it. This might be because the information needed about the cancer for each patient is not available at the time of making the treatment decision (for example, histological profiling of the cancer). The clinical experts explained that if the information needed about the cancer was available and the NSCLC was resectable, they would prefer to offer a neoadjuvant or perioperative approach.

Comparators

3.3 The company compared neoadjuvant pembrolizumab plus chemotherapy followed by surgery and then adjuvant pembrolizumab monotherapy (from now, perioperative pembrolizumab) with surgery alone, neoadjuvant chemotherapy and neoadjuvant nivolumab. The final scope for this evaluation also included neoadjuvant chemoradiotherapy (nCRT), platinum-based chemotherapy, perioperative durvalumab, adjuvant osimertinib, and adjuvant chemotherapy with or without atezolizumab maintenance treatment. The company decided that people having adjuvant treatment represented a slightly different population (people with complete resection) to those who might have a neoadjuvant or perioperative treatment (everyone with resectable disease). Also, people in the 2 populations would make treatment decisions at different times (before surgery compared with after surgery). So, the company did not consider adjuvant treatments to be relevant comparators. The company explained that it had not compared pembrolizumab with nCRT. This was because it is not widely used and would be used in a slightly different population (people with stage 3A cancer only) to those who might have perioperative pembrolizumab. The company also added that it did not consider that perioperative durvalumab was established in clinical practice, and so was not a relevant comparator. The NHS England CDF clinical lead advised that neoadjuvant nivolumab was the relevant comparator for this evaluation. This was because people would have neoadjuvant nivolumab unless they were ineligible, in which case they would also be ineligible for perioperative pembrolizumab. The clinical experts advised that for people eligible for immunotherapy, the treatment options would be neoadjuvant nivolumab or perioperative pembrolizumab (if recommended). The committee noted that

perioperative durvalumab was not recommended in routine commissioning and so was not a relevant comparator. It agreed that the adjuvant treatments were relevant to a different population (people having complete resection). It also agreed that the decision to have an adjuvant treatment may differ to the decision to have a neoadjuvant or perioperative treatment (see section 3.2). It concluded that adjuvant treatments were not direct comparators for this evaluation and the most relevant comparator was neoadjuvant nivolumab.

Clinical effectiveness

KEYNOTE-671 clinical trial evidence

3.4 The clinical evidence for perioperative pembrolizumab came from the KEYNOTE-671 randomised controlled trial. KEYNOTE-671 compared perioperative pembrolizumab with perioperative placebo (neoadjuvant chemotherapy and placebo followed by surgery and then adjuvant placebo). The interim analysis used by the company in its submission was from a July 2023 data cut and had a median follow up of 29.8 months and a maximum follow up of 62.0 months. The primary outcomes of the trial were:

- event-free survival (EFS), defined as the time from randomisation to an event that precluded surgery (including progression), disease progression after surgery or death
- overall survival (OS), defined as the time from randomisation until death.

The key secondary outcome from the trial was pathological complete response (pCR), defined as the absence of viable tumour cells in lung tissue and lymph node samples taken during surgery.

Pembrolizumab was associated with a statistically significant improvement in EFS compared with placebo, with a hazard ratio of 0.59 (95% confidence interval [CI] 0.48 to 0.72). It was also associated with a statistically significantly higher pCR rate than placebo, with 18.1% of people in the pembrolizumab arm having a pCR compared with 4.0% in the placebo arm, a difference of 14.2% (95% CI 10.1 to 18.7). OS was also statistically

significantly better for pembrolizumab than placebo with a hazard ratio of 0.72 (95% CI 0.56 to 0.93). Median OS was 52.4 months in the placebo arm but was not reached in the pembrolizumab arm. The company also presented EFS results for subgroups who did, and did not, have a pCR. The exact results are considered confidential by the company and cannot be reported here. The committee concluded that perioperative pembrolizumab was more effective than perioperative placebo at reducing both the risk of recurrence and of death.

Generalisability (age)

3.5 The EAG noted 2 generalisability concerns with KEYNOTE-671. The first was that the mean age in the trial was 63.1 years whereas the EAG's clinical expert estimated that the mean age of people with resectable NSCLC in NHS clinical practice would be 70 years. The EAG noted that immunotherapy might be less suitable for older people. It also noted that in a resectable stage oncology model that includes cure (see section 3.13), starting age has a substantial effect on accrued quality-adjusted life years (QALYs). The CDF clinical lead explained that, since NICE's technology appraisal guidance on nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer in March 2023, around 800 people have accessed neoadjuvant nivolumab, with a mean age of 67.5 years. The CDF clinical lead advised that the population who would access perioperative pembrolizumab would be very similar. The clinical experts added that the NHS targeted lung health check programme would likely result in more NSCLC being diagnosed at earlier stages and in younger people in the future. They advised it was reasonable to expect the mean age of patients to decrease over time. The committee agreed that it was plausible that the mean age would fall with time, but it noted that there was evidence that the current mean age in NHS practice was 67.5 years. It concluded that KEYNOTE-671 had a lower mean age than the potential NHS practice population, and that the modelling should reflect the NHS practice population (see section 3.10) to make the model results more generalisable to NHS practice.

Generalisability (treatment by pCR status)

3.6 The second generalisability concern was that in KEYNOTE-671 everyone had both neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) pembrolizumab. This was regardless of their response to the neoadjuvant component. Clinical advice to the company and included in its submission was that healthcare professionals in clinical practice were not likely to offer the adjuvant component to people who had a pCR (see section 3.4). This was because of concerns about overtreatment. The company submission included scenarios in which the costs of the adjuvant component were removed but with no adjustment to the relative efficacy. The EAG noted that the setup of KEYNOTE-671 did not allow assessment of the relative contributions of the neoadjuvant and adjuvant components. So, it decided the scenarios removing only costs were not useful for decision making. The clinical experts explained that people with a pCR at surgery tend to have very good outcomes. They noted that they might have limited benefit from the adjuvant component of pembrolizumab, but may have some of the rare but potentially serious adverse events that are associated with pembrolizumab treatment. But the clinical experts noted that there was no clinical evidence on this. They explained that people with a pCR are generally less likely to have progression, so a very large trial would be needed to clearly demonstrate any such benefits. A clinical expert advised there might be a second decision point after surgery, when people with a pCR and their healthcare professionals would weigh up the potential benefits and drawbacks and might decide not to continue with the adjuvant component of pembrolizumab.

The committee noted that KEYNOTE-671 was not designed to study how perioperative pembrolizumab would be used in NHS clinical practice, which brought uncertainty to the analysis. It decided that there was no evidence to inform the efficacy of the adjuvant component in people with a pCR, but that it was possible it would give no additional benefit. The committee noted it is likely that healthcare professionals would not offer the adjuvant component to everyone with a pCR in NHS practice, to avoid any adverse effects of continued immunotherapy. The committee decided that it was uncertain whether the relative effectiveness estimates of perioperative pembrolizumab should be adjusted to account for people with a pCR not having the adjuvant component. It concluded that the trial was not fully generalisable to NHS clinical practice. It noted that it was plausible that some people with a pCR would not have the

adjuvant component (noting that this might mean that costs for perioperative pembrolizumab in NHS practice would be lower than in the model). But the committee also noted that there may also be reduced health benefits for people not having the adjuvant component. The committee concluded that the model may overestimate both the health benefits and costs of perioperative pembrolizumab compared with NHS clinical practice, but this was uncertain. It agreed modelling perioperative treatment costs and benefits, as in the trial, was appropriate.

Reporting and comparison of outcomes

3.7 The EAG noted that there was only indirect evidence available for the outcome of EFS for comparisons with all modelled comparators. It highlighted that the scope included several other outcomes that had not been compared. These included pCR, adverse events, health-related quality of life and OS. The company clarified that these outcomes did not drive the model. It also noted that feasibility assessments meant that indirect comparisons of adverse events and health-related quality of life were not possible because of differences in the way the different studies reported these. It explained that the OS data was too immature to allow a reliable indirect comparison. The EAG advised that OS was an important outcome and that it could not make a full assessment of the relative effectiveness of perioperative pembrolizumab compared with neoadjuvant nivolumab in the absence of an indirect comparison.

The professional organisation submission stated that EFS was recognised as a reasonable surrogate for OS. The clinical experts explained that it was very difficult to comment on the relative effectiveness of perioperative pembrolizumab compared with neoadjuvant nivolumab for OS because of the lack of a head-to-head trial or reliable indirect treatment comparison (see section 3.8). But they noted that KEYNOTE-671 showed a significant OS advantage of perioperative pembrolizumab compared with perioperative placebo (see section 3.4) and that the current data cut of the CheckMate-816 trial had not reported a significant OS advantage for neoadjuvant nivolumab. A clinical expert explained that in some people, 3 cycles of neoadjuvant nivolumab might not provide a durable response, whereas the additional cycles of the perioperative pembrolizumab regimen might boost response and duration of response, and this might lead to an OS gain. The

clinical experts agreed that EFS was a reasonable surrogate for OS and advised it is likely that perioperative pembrolizumab would have an OS advantage compared with neoadjuvant nivolumab. But they noted the lack of clinical evidence to support this.

The company had validated the modelled OS by comparing it with OS from KEYNOTE-671 and a cohort from the real-world SEER-Medicare database. But, the committee noted that this validation was only done for perioperative pembrolizumab and neoadjuvant chemotherapy. It noted that because neoadjuvant nivolumab was the main comparator (see section 3.3) it was important to validate its modelled OS. The committee noted that it would have preferred relative effect estimates for OS for perioperative pembrolizumab compared with neoadjuvant nivolumab, ideally to drive the model. As a minimum, the committee would have expected to see evidence to show that changes in EFS were associated with proportionate changes in OS. It noted that it had only heard clinical expert testimony to support the surrogate relationship between EFS and OS. It decided that it was plausible to assume that the EFS benefits estimated by the indirect treatment comparison (see section 3.8) might translate into an OS benefit, but that this, and the size of any OS benefit, was very uncertain. It considered that using EFS as a surrogate for OS in the modelling was acceptable. But, it concluded that this assumption was associated with substantial uncertainty because of the lack of direct or indirect evidence on the relative OS effect.

Indirect treatment comparison results for EFS

3.8 There was no head-to-head comparison of perioperative pembrolizumab with neoadjuvant nivolumab or surgery alone, so the company did network meta-analyses (NMAs). These compared perioperative pembrolizumab (KEYNOTE-671 trial) with neoadjuvant nivolumab (CheckMate-816 trial) using the common comparator of neoadjuvant chemotherapy for the outcome of EFS. CheckMate-816 compared neoadjuvant nivolumab plus chemotherapy with neoadjuvant chemotherapy alone. It had a published median follow up of 29.5 months and maximum follow up of 41.4 months. The company submitted 2 types of NMA, 1 with time-varying and 1 with time-constant hazard ratios. Each was fitted using both fixed and random effects models. The time-constant NMA

returned a hazard ratio of 0.87 (95% credible interval [CrI] 0.59 to 1.27) for the fixed effects model and 0.87 (95% CrI 0.10 to 7.27) for the random effects model. The fixed effects time-varying NMA returned a range of hazard ratios from the 3-month time point (1.30, 95% CrI 0.72 to 2.36) to the 60-month time point (0.60, 95% CrI 0.33 to 1.10), with the hazard ratio gradually decreasing as time went on. The random effects time-varying NMA returned similar results but with wider credible intervals. The committee noted that the time-varying NMA was only based on observed data up to the 48-month time point. It noted the relatively wide credible intervals in both the time-varying and time-constant NMAs. The committee concluded that the NMAs showed varying levels of numerical advantage for perioperative pembrolizumab compared with neoadjuvant nivolumab. It further concluded that none of these reached statistical significance and that the relative effectiveness of perioperative pembrolizumab compared with neoadjuvant nivolumab was associated with uncertainty.

Choice of indirect treatment comparison for EFS

3.9 The company used the time-varying fixed effects NMA for EFS in its base case. It did this because it considered it standard practice in cancer evaluations to model within-trial survival curves independently, and so it would be appropriate to model inter-trial curves independently. It also decided that it was biologically plausible that the hazard ratio between perioperative pembrolizumab and neoadjuvant nivolumab would change over time, for 2 reasons. Firstly, because of differences in timing of surgery (people having perioperative pembrolizumab will have surgery around 3 weeks later than people having neoadjuvant nivolumab). Secondly, because of the added effects of the adjuvant component of perioperative pembrolizumab. The company acknowledged that there was no evidence that the proportional hazards tests had been violated, but explained that they were only powered to detect the most pronounced violations of the proportional hazards assumption. The company also explained that although a time-varying hazard ratio relaxed the proportional hazards assumption, it still allowed for proportional hazards to be modelled if the data showed such a trend. The EAG clinical expert advised that the biological plausibility of time-varying hazards was unknown. The EAG explained that because there was no evidence that the proportional hazards assumption had been violated, a time-constant NMA was an appropriate starting point. The EAG used the time-constant NMA in

its base case. A clinical expert emphasised that it was important to recognise the effect that the adjuvant component might have for many people (see section 3.6). The committee decided that it was biologically plausible that the hazard ratios might vary over time. This is because of the timing of surgery, the extra cycle of neoadjuvant treatment and the additional adjuvant component of pembrolizumab, and that it would be difficult to justify assuming proportional hazards. It noted that there was substantial overlap in credible intervals between the time-constant and time-varying hazard ratios. But it decided that the fact the credible intervals were similar in the time-varying NMA was not a substantial issue. The committee recalled that both NMAs were uncertain (see section 3.8) but concluded that it preferred to use the results of the time-varying NMA to inform the relative effectiveness of neoadjuvant nivolumab and perioperative pembrolizumab on EFS.

Economic model

Company's modelling approach

3.10 The company constructed a state-transition model with 4 health states to model the cost effectiveness of perioperative pembrolizumab compared with the comparators. The health states were event free (EF), locoregional recurrence or progression (LR-P), distant metastases (DM), and death. People in the model started in the EF health state and could either move to LR-P or DM. From LR-P people could move to DM, and people could move to the death state from any of the other health states. The model included a cure assumption, which meant that a proportion of people in the EF health state at a given time point would be considered cured (see section 3.13). People in the model accrued QALYs, treatment costs and healthcare resource use costs depending on which treatments they had and which health states they spent time in. The intervention arms of the model (perioperative pembrolizumab or neoadjuvant nivolumab) did not affect the efficacy of subsequent treatments or the costs or utilities generated in subsequent health states. They only informed transitions into subsequent health states and affected what types of treatment people could have in them because of immunotherapy retreatment considerations. The model assumed that people who had progression at least 6 months after the last dose

of immunotherapy in the adjuvant or neoadjuvant setting could have retreatment with an immunotherapy. The CDF clinical lead confirmed that this retreatment would reflect NHS clinical practice. The committee recalled the mean age in NHS clinical practice (see section 3.5) and concluded that the model starting age should be set to 67.5 years. It also recalled that the model did not directly use OS and relied on a surrogate relationship between EFS and OS, noting that the extent of this relationship was uncertain (see section 3.7). But it decided that, in the absence of a model directly incorporating the relative effectiveness of OS, the model structure was acceptable for decision making.

Modelling event-free survival

3.11 To model health state occupancy for the EF state the company used EFS curves from KEYNOTE-671. The curves were censored for events not of interest. For example, to derive the EF to LR-P curve, all distant metastatic and death events were censored. The 3 curves were then extrapolated to the time horizon of the model, using the generalised gamma distribution for the EF to LR-P and DM curves and the log-normal distribution for the EF to death curve. The hazard ratios from the time-varying NMA (see section 3.8) for each comparator were applied to the perioperative pembrolizumab EFS curve to generate comparator EFS curves. The breakdown of EFS events between the LR-P, DM and death states was assumed to be the same for the comparators as for perioperative pembrolizumab. These curves were used to calculate per-cycle transition probabilities out of the EF state to the other health states. The committee noted that transitions out of the EF state had a very large influence in the model and were based on relatively immature data, and it recalled the substantial remaining uncertainty around how long treatment effect should continue (section 3.12) and the modelling of cure (see section 3.13). It concluded that in the absence of more mature evidence that would have reduced the uncertainty around transitions out of the EF state, the modelling approach was acceptable for decision making.

Treatment effect waning

3.12 The company base case used the time-varying hazard ratio (see section 3.9) applied until 62 months (the maximum follow up of KEYNOTE-671). After this

point it carried the final hazard ratio from the fixed effects time-varying NMA forward to the end of the model. The EAG advised that this might overestimate the benefit of perioperative pembrolizumab and that there was no evidence for a sustained EFS effect of perioperative pembrolizumab over neoadjuvant nivolumab. The EAG base case set the hazard ratio for perioperative pembrolizumab compared with neoadjuvant nivolumab to 1.0 from 41.4 months, which was the maximum follow up in CheckMate-816. The company responded that if treatment effect waning (setting the hazard ratio to 1) were to be modelled then it should be done in line with previous evaluations of immunotherapies in which the hazard ratio gradually moves to 1 over time. It submitted a scenario in which this occurred between 5 and 7 years.

A clinical expert explained that response to immunotherapies would differ between people, and it was difficult to say whose NSCLC might respond in which way. Some people might have had a durable response to immunotherapy that persisted well beyond the treatment period. They noted that some people with advanced or metastatic NSCLC had disease control for many years after stopping treatment. But they noted that there would be some people for whom the treatment effect would stop after finishing treatment. The clinical experts summarised that, on balance, it might be appropriate to model some treatment effect waning for the whole population.

The committee noted that the treatment effect had the biggest effect on the model before the cure point (section 3.13). It also noted that treatment effect would likely disappear at the cure point, because the small number of people who were not cured at this point were unlikely to be getting an indefinite treatment effect. The committee decided that it would not be appropriate to model a constant treatment effect for perioperative pembrolizumab for the lifetime of the model. It considered that some form of treatment effect waning assumption should be applied, although it acknowledged there was little evidence to inform this. The committee decided that it was appropriate to apply a treatment effect waning assumption from the end of the observed data (41.4 months), but that it would be inappropriate to set the hazard ratio to 1 instantaneously. Instead, the committee preferred to apply a gradual treatment effect waning over 2 years, noting that this was in keeping with previous assumptions used in evaluations of immunotherapies for NSCLC. The committee concluded that it was appropriate to apply a gradual treatment effect waning starting at 3.5 years and ending at

5.5 years.

Cure assumptions

3.13 The company model contained the assumption that 95% of people in the EF health state were considered cured at 7 years. The proportion rose from 0% at 5 years to 95% at 7 years. People considered cured no longer moved out of the EF state and were assumed to have age- and sex-matched general population mortality. The EAG clinical expert advised that the risk of recurrence beyond 5 years was generally very low, and that diagnosis of NSCLC after 5 years was likely to be treated as a primary cancer. The clinical expert agreed that the risk of recurrence was very low after 5 years. They noted that the exact time point and proportions were uncertain but advised that many people whose disease had not recurred by 5 years could be considered cured. The committee would have preferred to see modelling of a cure assumption based directly on clinical evidence, and if this was impossible it would have preferred calibration of the cure proportion to late recurrence estimates from an external study. But it acknowledged that the cure proportion and point had a limited effect on the estimates of cost effectiveness. It decided that there was uncertainty in this element of the model but concluded that it could use the company's modelling of cure point and proportion in its decision making.

Modelling mortality after cure

3.14 The EAG noted that there was some evidence in the literature that people considered cured might have higher mortality than the general population. So the EAG calculated a standardised mortality ratio (1.453) from an external study and applied it to general population mortality to represent the higher risk of mortality in the cured population, and included it in its base case. The clinical experts agreed that people who have had NSCLC would not have the same mortality as the general population. One reason for this was that a high proportion of people with NSCLC smoke or have smoked, and these people might have other comorbidities such as cardiovascular disease and cerebrovascular disease which are associated with increased mortality. The committee decided it was unlikely that people who were considered cured would have the same mortality as the

general population. It agreed with the concept of applying a standardised mortality ratio to reflect the additional risk of mortality. It noted that there was uncertainty around the exact value that should be used but concluded that the EAG's standardised mortality ratio of 1.453 was acceptable to use for decision making.

Modelling locoregional progression or recurrence

3.15 People in KEYNOTE-671 were not followed up with imaging once they had experienced locoregional progression so it was not possible to model transitions out of the LR-P state from the KEYNOTE-671 data. The company identified a cohort of 43 people from the SEER-Medicare database (a large cancer database that combines data of people with cancer with Medicare claims) who it considered to have patient characteristics aligned with the KEYNOTE-671 population. Exponential competing risks models were fitted to cause specific transitions from LR-P to DM or death in this cohort. This gave a constant weekly rate by which people would transition to DM or death, and this rate was constrained so that it did not fall below general population mortality. The transition probabilities from this health state were applied equally to people in all arms of the trial. The committee noted that the modelling of locoregional progression or recurrence was likely a simplification of what would occur in NHS clinical practice. But, it noted that it affected both arms of the model in a similar way and did not appear to have a substantial effect on the cost-effectiveness estimates. It concluded that the modelling of locoregional progression was acceptable for decision making.

Modelling distant metastases

3.16 The company modelled transitions from the DM health state to the death health state by calculating weekly rates of progression-free survival (PFS) and OS for all subsequent treatments used as first-line treatments for metastatic disease. The weekly rates were calculated from the median PFS and OS reported from trials that originally assessed the subsequent treatments. Estimates of market share for each comparator were used to generate a weighted weekly rate of PFS and OS events. The weighting depended on how many people were eligible for

retreatment with immunotherapies in the DM health state (see section 3.10). The ratio of OS to PFS events was used to calculate how many people in the DM health state had progression-free or progressed disease and to calculate total healthcare resource use costs and utility. Costs in the progressed disease portion of the DM health states were based on market share estimates for second-line treatments in the metastatic health state, but OS was only affected by the first-line treatment. The committee noted that beyond differences in retreatment (section 3.10), which would occur because perioperative pembrolizumab treatment is longer than neoadjuvant nivolumab treatment, the modelling of the DM health state did not have a large effect on the cost-effectiveness estimates. It concluded that the modelling of the DM health state was appropriate for decision making.

Utility values

Utility in the model

3.17 The company used utility estimates from KEYNOTE-671 to inform utility values in the model for the EF (0.882 [without adverse events]), LR-P (0.776) and DM (pre-progression, 0.727) health states. There was insufficient data from KEYNOTE-671 to inform the DM (post-progression) health state utility value. So, the company used health-related quality of life data from the KEYNOTE-189 and KEYNOTE-407 trials to estimate utility for people with non-squamous (0.657) and squamous (0.679) NSCLC, respectively. These utility values were weighted by the proportions of people in KEYNOTE-671 with non-squamous (56.8%) and squamous (43.2%) disease. Utility values in the model were adjusted for age and sex. The EAG noted that the utility value in the EF health state was higher than the age- and sex-matched utility value estimate for the general population (0.822). It provided a scenario in which the EF health state utility was capped at the general population utility value. The committee decided that it was not realistic to model a utility value for people with NSCLC that was higher than the utility value for the general population. It concluded that utility in the EF health state should be capped at the level of the general population.

Cost-effectiveness estimates

Acceptable ICER

3.18 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, specifically around:

- the issue of generalisability between the way perioperative pembrolizumab was used in KEYNOTE-671 and would be used in NHS practice (see section 3.6)
- the uncertainty in the results of the indirect treatment comparisons (see sections 3.8 and 3.9)
- the absence of relative effectiveness estimates for OS and the extent of the surrogate relationship between EFS and OS (see section 3.7)
- modelling of the assumptions of cure and the mortality rate used for cured people (see sections 3.13 and 3.14).

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

The committee's preferred assumptions

3.19 The committee recalled its preferences for the cost-effectiveness modelling of perioperative pembrolizumab including:

- using neoadjuvant nivolumab as the main relevant comparator (see section 3.3)

- using a time-varying NMA to inform relative effectiveness of perioperative pembrolizumab compared with neoadjuvant nivolumab (see section 3.9)
- modelling a treatment effect waning assumption that set the EFS hazard ratio for perioperative pembrolizumab and neoadjuvant nivolumab to 1 between 3.5 and 5.5 years (see section 3.12)
- setting the model starting age to 67.5 years (see section 3.10)
- applying a cure assumption in which 0% of people were considered cured at 5 years, rising to 95% at 7 years (see section 3.13)
- applying a standardised mortality ratio of 1.453 to general population mortality to reflect the higher mortality of the cured population (see section 3.14)
- limiting utility in the EF health state to the age- and sex-matched general population utility value (see section 3.17).

  The ICER when applying the committee's preferred assumptions was at the lower end of the range normally considered an acceptable use of NHS resources (£20,000 to £30,000 per QALY gained). The exact ICERs are confidential and cannot be reported here because of confidential discounts for technologies included in the modelling.

Other factors

Equality

3.20 The committee did not identify any equality issues.

Uncaptured benefits

3.21 The committee considered whether there were any uncaptured benefits of perioperative pembrolizumab. It recalled the possibility that there were costs in

the model that would not occur in NHS clinical practice, but also that there may be health benefits in the model that may not occur in NHS clinical practice (see section 3.6). It concluded that it could not consider this as an uncaptured benefit because there was no evidence provided to estimate the size and direction of its impact on the cost-effectiveness estimates.

Conclusion

Recommendation

3.22 The committee took into account its preferred assumptions and the key uncertainties in the model. It concluded that the most plausible ICER was within the range that NICE considers an acceptable use of NHS resources. So, perioperative pembrolizumab is recommended for routine commissioning.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has resectable non-small-cell lung cancer that is at high risk of recurrence and the healthcare professional responsible for their care thinks that perioperative pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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

Megan John
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 and a project manager.

Samuel Slayen
Technical lead

Adam Brooke
Technical adviser

Celia Mayers
Project manager

Lorna Dunning and Jasdeep Hayre
Associate directors

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