NICE National Institute for Health and Care Excellence

NICE guidance

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

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 as an option for untreated metastatic colorectal cancer with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency in adults, only if:

- pembrolizumab is stopped after 2 years and no documented disease progression, and
- the company provides pembrolizumab according to the commercial arrangement.

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 clinician consider it appropriate to stop.

Why the committee made these recommendations

People with untreated metastatic colorectal cancer that has high MSI or MMR deficiency are usually offered combination chemotherapy including FOLFOX, FOLFIRI or CAPOX. For RAS wild-type cancer, cetuximab or panitumumab is added to FOLFOX or FOLFIRI.

Clinical trial evidence shows that pembrolizumab increases the time until the condition gets worse compared with current treatments. Pembrolizumab may also be more effective at extending life, but the evidence is limited and in the trial people had subsequent treatments that are not available in the NHS. So, it is uncertain how much benefit it offers over a person's lifetime.

There is no evidence from clinical trials that use pembrolizumab for more than 2 years of treatment so the benefit beyond this duration is uncertain.

The cost-effectiveness estimates are within what NICE normally 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) has a marketing authorisation as monotherapy 'for the first-line treatment of metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer in adults'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of pembrolizumab is £2,630 per 100-mg vial (excluding VAT; BNF online, accessed March 2021). The cost of a single administration is £5,260. This represents 3 weeks of treatment.

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. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Merck Sharp and Dohme, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- Subsequent treatment costs in the model should not include cetuximab because it is not recommended after first-line treatment in the NHS.
- Time-on-treatment for panitumumab with FOLFOX in the model should equal time-on-treatment for standard care in KEYNOTE-177.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see ERG report, table 1, page 18), and took these into account in its decision making. It discussed issues 1 to 5, which were outstanding after the technical engagement stage.

The condition

There is an unmet need for treatments for high microsatellite instability or mismatch repair deficiency metastatic colorectal cancer

3.1 Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Mutations can cause microsatellite instability (MSI) or DNA mismatch repair (MMR) deficiency in some metastatic colorectal cancer cells. DNA MMR corrects errors that occur during DNA replication, so problems with DNA MMR can lead to mutations in the microsatellites (repetitive DNA sequences). This causes them to become unstable, resulting in cancerous tumours with high MSI. High MSI or DNA MMR deficiency occurs in around 4% of metastatic colorectal cancer. It is associated with a poorer prognosis and a greater risk of death than metastatic colorectal cancer without MSI. There are

currently no specific treatments for this type of colorectal cancer, so people are offered the same treatment whether or not their colorectal cancer has high MSI or DNA MMR deficiency. The committee concluded that there is an unmet need for treatments for this condition.

People with the condition and clinicians would welcome new treatment options

3.2 The patient experts explained that a diagnosis of metastatic colorectal cancer with high MSI or DNA MMR deficiency affects quality of life both physically and psychologically. They highlighted that current treatments were highly toxic, which could lead to hospital admissions during treatment and permanent adverse effects like nerve damage. They explained that having progressed on several different treatments, their cancers had responded well to pembrolizumab, which was life changing. The committee noted that pembrolizumab, a checkpoint inhibitor, worked in a different way to chemotherapy. It heard that people appreciated the faster and less frequent administration of pembrolizumab, and preferable adverse effects compared with standard care. A clinical expert explained that, with a more effective treatment, there was potential that a patient's condition would respond well enough for them to have surgery with curative intent. The committee concluded that people with the condition and clinicians would welcome new treatment options.

The treatment pathway

Current standard care for metastatic colorectal cancer depends on fitness, RAS mutation, clinician judgement and the patient's informed preferences

3.3 Clinical experts explained that there are several first-line treatment options for metastatic colorectal cancer. Individualised treatment pathways are common and consider potential impacts of first-line treatment on available subsequent therapies because of the limited number of options for this cancer. Clinical experts explained that, because of the high toxicity of many standard care treatments, a patient's clinical status and performance status (their ability to complete

daily tasks and ordinary activities), along with any comorbidities, would impact clinicians' judgement on the most suitable treatments. For example, people who are less frail would be offered more intense combinations according to the clinical evidence. A patient expert highlighted that people might also decline some chemotherapy regimens to avoid toxic side effects. The committee noted that first-line treatment options are limited by whether a mutation in the RAS gene is present. The committee concluded that current standard care for metastatic colorectal cancer with high MSI or DNA MMR deficiency depends on fitness, RAS mutation status, clinician judgement and the person's informed preferences.

Most people have combination chemotherapy at first line

3.4 Clinical experts explained that most people with untreated colorectal cancer have combination chemotherapy, usually with: folinic acid; fluorouracil (5 FU) and oxaliplatin (known as FOLFOX); 5 FU, folinic acid and irinotecan (known as FOLFIRI); or capecitabine and oxaliplatin (known as CAPOX). Clinical experts discussed the effectiveness of these regimens, noting that they are used interchangeably in clinical practice and are considered equivalent. The committee heard that, to increase the chance of good clinical outcomes, a small proportion of people with RAS-mutant disease would have FOLFOXIRI (folinic acid, 5 FU, oxaliplatin and irinotecan). But, because of the higher toxicity of the combination, this would only be offered to fitter people. The committee concluded that FOLFOX, FOLFIRI, FOLFOXIRI and CAPOX were relevant comparators at first line.

People with RAS wild-type colorectal cancer would have cetuximab or panitumumab in combination with either FOLFOX or FOLFIRI

3.5 Clinical experts explained that people with cancers with no mutation in the RAS gene (referred to as RAS wild-type) would be offered an epidermal growth factor receptor (EGFR) inhibitor in addition to chemotherapy with FOLFOX or FOLFIRI. This is in line with NICE's technology appraisal guidance on cetuximab and panitumumab for previously untreated metastatic colorectal cancer. The committee heard

that cetuximab is used only in tumours that also express the EGFR protein, and noted that this is not a requirement for panitumumab. Clinical experts explained that, if recommended, pembrolizumab would be the preferred option for people with colorectal cancer regardless of RAS status, because of the poor outcomes for people with high MSI or DNA MMR-deficient disease. The clinical experts acknowledged this meant EGFR inhibitors would not be used for this population because their recommendation is limited to first-line treatment. The committee concluded that, in current clinical practice, people with RAS wild-type tumours would have cetuximab or panitumumab in combination with either FOLFOX or FOLFIRI.

Capecitabine is used less commonly than other treatments, but is a relevant comparator for some people

3.6 Although listed in the NICE scope as a comparator, the company did not include capecitabine, raltitrexed or tegafur with uracil in its submission. NICE's technology appraisal guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer recommends capecitabine monotherapy as an option for untreated metastatic colorectal cancer. Clinical experts explained that capecitabine is used only in people with a poor performance status (Eastern Cooperative Oncology Group [ECOG] score of 2 or more), who are likely to be frail and so cannot tolerate the toxicities of combination chemotherapy. Clinicians noted that they would be unlikely to use a monotherapy to treat high MSI or DNA MMR-deficient colorectal cancer because of the poor outcomes of monotherapy and poor prognosis in this population. However, capecitabine monotherapy would be appropriate if the person had a very low performance status. One clinical expert estimated that capecitabine would be used in less than 10% of people with high MSI or DNA MMR-deficient tumours. However, the committee considered that, although likely to be small in clinical practice, the population who would have capecitabine would also be able to have pembrolizumab. It was aware that the summary of product characteristics for pembrolizumab allows treatment of people with an ECOG status of 2 and above 'after careful consideration of the potential increased risk' and 'with appropriate clinical management'. The committee concluded that capecitabine may be used less commonly than other treatment options

but is a relevant comparator for a small group of people and may be less effective than combination therapies.

Tegafur with uracil and raltitrexed are not relevant comparators for pembrolizumab

3.7 The company excluded tegafur with uracil and raltitrexed as comparators in its submission, despite having been included in the NICE scope. Clinical experts confirmed that tegafur with uracil was not available in the NHS in England and did not consider it relevant as a comparator. The committee also heard that although raltitrexed is used in clinical practice, it is reserved for specific indications, such as people with a history of heart disease or who develop angina on 5 FU-based chemotherapy. However, because it has a marketing authorisation for first-line use only, pembrolizumab would not be used in people who develop side effects on chemotherapy. The committee agreed that the population who would receive raltitrexed in clinical practice and could also receive pembrolizumab is negligible. It concluded that tegafur with uracil and raltitrexed are not relevant comparators for pembrolizumab in untreated metastatic colorectal cancer with high MSI or DNA MMR deficiency.

Testing

Although routinely funded, not all people newly diagnosed with colorectal cancer are tested for high MSI or DNA MMR deficiency in the NHS

3.8 NICE's diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer recommends testing all people with colorectal cancer to identify DNA MMR-deficient tumours. This can be done either by immunohistochemistry testing for MMR proteins or polymerase chain reaction for determining MSI. Clinical experts noted variation in local uptake for high MSI or DNA MMR deficiency testing across the NHS, which was supported by testimonials from the patient experts. However, the clinical lead for the Cancer Drugs Fund confirmed that this testing is routinely commissioned by NHS England. It was explained that uptake is currently low in some places, but

it is increasing. They clarified that testing should be offered to all newly diagnosed people before starting treatment. The committee noted that nivolumab and pembrolizumab are already available as interim treatment options during the COVID-19 pandemic for untreated colorectal cancer with high MSI or DNA MMR deficiency. So, the committee was aware that treatment decisions in the NHS are already being made based on the results of these tests. The committee agreed that it is correct to exclude the costs of testing for high MSI or DNA MMR deficiency from the company's model, because the tests are already routinely done by the NHS. It concluded that the costs associated with pembrolizumab need not include the costs for testing for high MSI or DNA MMR deficiency. It further concluded that if pembrolizumab is used routinely, then the NHS would need to improve testing uptake in some places.

Clinical evidence

Clinical evidence for pembrolizumab comes from the KEYNOTE-177 trial, but the control treatments used in the trial do not reflect NHS practice

3.9 KEYNOTE-177 is a multinational, open-label, randomised, phase 3 trial, comparing pembrolizumab with standard care. It included only people with inoperable untreated metastatic colorectal cancer with high MSI or DNA MMR deficiency. The primary outcomes were progression-free survival and overall survival. Standard care was defined by the company as investigator's choice of:

- FOLFOX
- FOLFIRI
- cetuximab with FOLFOX or FOLFIRI
- bevacizumab with FOLFOX or FOLFIRI.

The company pooled data from all standard care regimens in its comparison with pembrolizumab. This means that there are no data directly comparing pembrolizumab with each separate regimen in the standard care control arm.

Clinical experts explained that the control arm of KEYNOTE-177 did not accurately reflect clinical practice in the NHS. This was because the trial excluded first-line treatment options for metastatic colorectal cancer in the NHS, including CAPOX and FOLFOXIRI, and for RAS wild-type tumours, panitumumab with FOLFOX or FOLFIRI. Moreover, the KEYNOTE-177 trial included bevacizumab in the control arm, but NICE does not recommend bevacizumab at first line in this population (see NICE's technology appraisal guidance on bevacizumab and cetuximab for the treatment of metastatic colorectal cancer and bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer). The committee concluded that the comparators used in the trial are not entirely reflective of NHS practice.

Bevacizumab likely offers a benefit to patients, so the trial may underestimate the relative effect of pembrolizumab compared with standard care

3.10 Around 70% of people randomised to standard care in KEYNOTE-177 had bevacizumab-containing regimens. The clinical lead from the Cancer Drugs Fund explained that bevacizumab is likely to benefit people with colorectal cancer with high MSI or DNA MMR deficiency. However, there are limited data available for this population, so the extent of any benefit is unknown. The ERG explained that, if bevacizumab were more effective than other available treatments, the results from the KEYNOTE-177 may underestimate the relative effectiveness of pembrolizumab in the trial compared with in the NHS. A clinical expert agreed that bevacizumab is effective and noted that, unlike cetuximab and panitumumab, its use was not limited by RAS status. The committee noted that the KEYNOTE-177 trial included some people from outside the UK and that not all of those included in the trial had the RAS status of their tumours determined before treatment. A clinical expert involved in the trial explained all UK participants had a documented RAS status and this determined their treatment options. However, he noted that some participants outside the UK with undetected RAS wild-type tumours may not have had cetuximab or panitumumab with FOLFOX or FOLFIRI as they would have in the NHS. Instead, they had bevacizumab or combination chemotherapy. The committee appreciated that this might overestimate the effectiveness of pembrolizumab relative to standard care in the trial compared with in the

NHS. The committee recalled that standard care in KEYNOTE-177 was not representative of treatment options in the NHS as bevacizumab is not available in England. The company conducted an exploratory analysis for primary outcomes of progression-free survival and overall survival that excluded people who had bevacizumab combination treatments in the standard care arm. The ERG and clinical experts noted that the proportion of the population included in the company's scenario was small (32% of the trial population) and therefore excluded some data, and also broke the trial's randomisation. So, the committee did not consider the scenario further. The committee appreciated that the standard care arm included multiple treatments. So, pooling these treatments across a population meant a blended comparator was being used to determine the efficacy results of pembrolizumab. The committee was aware that the components of the blended comparator have different degrees of benefit, and that using a blended comparator approach averages the clinical effectiveness of the included treatments. The committee agreed that including a blended comparator in the estimates of clinical effectiveness makes the results more uncertain. It concluded that bevacizumab likely offers a small benefit to patients, so the trial may underestimate the relative effect of pembrolizumab compared with standard care. But, it might also overestimate the relative effect because some people in the control arm may not have had the best treatment for their condition. The committee concluded that there is some uncertainty in the results.

Pembrolizumab extends progression-free survival

3.11 The primary outcomes in the KEYNOTE-177 trial were progression-free survival and overall survival. Intention-to-treat analyses showed that pembrolizumab increased progression-free survival by 40% compared with standard care (hazard ratio 0.60, 95% confidence interval [CI] 0.45 to 0.80). Results for overall survival also favoured pembrolizumab; 37% of people taking pembrolizumab died compared with 45% of people taking standard care (hazard ratio 0.77, 95% CI 0.54 to 1.09). However, the committee noted the low number of deaths and that the median follow up was 28 months at the data cut-off point, so the overall survival data were immature. In addition, the KEYNOTE-177 trial allowed people who progressed on standard care to crossover to take pembrolizumab. The

committee noted that 36% of people taking standard care crossed over to pembrolizumab and a further 23% had an alternative checkpoint inhibitor after progression. Therefore, the overall survival results were likely to underestimate the relative treatment effect of pembrolizumab compared with standard care. The committee concluded that, based on the KEYNOTE-177 results, pembrolizumab likely extends progression-free survival compared with standard care but that the extent of any benefit on overall survival is uncertain.

Pembrolizumab may be less effective in people with RAS-mutant disease, but results are uncertain

3.12 Company analyses of progression-free survival in subgroups from the KEYNOTE-177 trial suggested a different effect for pembrolizumab for people with RAS-mutant disease compared with RAS wild-type. Results for people with colorectal cancer with high MSI or DNA MMR deficiency who had RAS-mutant disease showed no effect for pembrolizumab (hazard ratio 1.19, 95% CI 0.68 to 2.07). The clinical experts highlighted that there was no biological explanation for a poor response in the RAS-mutant subgroup. The company explained that the number of people with RAS-mutant disease in the subgroup analysis was small and that the confidence intervals included the possibility of a benefit. Also, the subgroup was not prespecified in the KEYNOTE-177 trial. The committee was aware of analyses done by the regulator, the European Medicines Agency. This included Kaplan–Meier data by subgroup that appeared to show a difference in effectiveness based on RAS status. However, the committee appreciated that the licence included people with RAS-mutant tumours. Clinical experts explained that subgroup analyses of other checkpoint inhibitors had not suggested a different effect by RAS status, although the data were not for first-line treatments. The ERG noted that 27% of the population did not have a RAS status confirmed in KEYNOTE-177 and that these people had been excluded from the subgroup analyses. The committee recalled that treatment decisions in the NHS are determined by RAS status so treatments in KEYNOTE-177 did not reflect standard care in the NHS. The committee concluded that there were limited data available for people with RAS-mutant disease and the subgroup analyses were not prespecified and included small sample sizes. Therefore, the effectiveness of pembrolizumab in people with

RAS-mutant disease is uncertain.

Subsequent treatments in KEYNOTE-177 do not reflect NHS clinical practice but may extend life

3.13 The committee recalled that over half the people in KEYNOTE-177 randomised to the standard care arm had checkpoint inhibitors after progression. The committee also noted 24% of those in the standard care arm who had subsequent treatment with pembrolizumab did so before disease progression. The committee was aware that checkpoint inhibitors are not available at second line and beyond in the NHS and may extend life compared with current clinical practice. The clinical experts also explained that the KEYNOTE-177 trial included cetuximab as a subsequent therapy, which is not recommended after first line in the NHS. A further consideration was raised that people in the pembrolizumab arm who stopped treatment before 2 years could have a further 17 cycles after progression. Clinical experts explained that the number of people who were retreated was less than 3%. The committee concluded that subsequent treatments in the KEYNOTE-177 trial did not reflect those in the NHS, but may extend life, which may underestimate the relative effectiveness of pembrolizumab. The committee agreed that the modelling of cost effectiveness should reflect this.

Pembrolizumab is likely better tolerated than standard care, but the company has not included some rare serious adverse events in the economic modelling

3.14 In KEYNOTE-177, a greater proportion of people had a serious adverse event in the standard care arm compared with the pembrolizumab arm (52% and 41%, respectively). The committee heard from patient experts that the side effects of chemotherapy had significantly impacted their quality of life, causing fatigue, sickness and diarrhoea for 1 week after every cycle. In contrast, they had experienced minimal side effects during treatment with pembrolizumab. Although a patient expert developed immune-based complications including rheumatoid arthritis and ulcerative colitis, he preferred these to the adverse effects of standard care. The committee noted that the proportion of people who

had at least 1 adverse event of any severity when taking pembrolizumab in the KEYNOTE-177 trial was high (97% for pembrolizumab compared with 99% for standard care). It heard that the company had included in its model only adverse events that were graded severe and occurred in over 5% of people. The clinical lead for the Cancer Drugs Fund raised concerns that immunotherapies can cause serious adverse events in a small number of people, and that, using the company's approach, these would not have been captured in the economic modelling. The committee concluded that pembrolizumab has an acceptable adverse event profile, but that the company omitted some rare serious adverse events from its economic modelling.

Indirect treatment comparison

FOLFOX, FOLFIRI and CAPOX are equally effective

3.15 There are no head-to-head trials that compare pembrolizumab with relevant comparators: CAPOX and panitumumab with FOLFOX or FOLFIRI. Therefore, the company compared them indirectly using a network meta-analysis. The committee recalled that the KEYNOTE-177 standard care arm pooled all treatments, so there were no data in the high MSI or DNA MMR-deficient population specific to each comparator, including FOLFOX or FOLFIRI. It also noted that the company's network meta-analysis assumed that FOLFOX and FOLFIRI were clinically equivalent. The committee noted that NICE's technology appraisal guidance on cetuximab and panitumumab for previously untreated metastatic colorectal cancer assumed that FOLFOX and FOLFIRI were broadly equivalent. In their base cases, both the ERG and company also assumed that the effectiveness of CAPOX was equivalent to FOLFOX and FOLFIRI. This was because results from the literature reported similar median progression-free survival and overall survival for CAPOX compared with FOLFOX and FOLFIRI. Clinical experts explained that FOLFOX, FOLFIRI and CAPOX treatments are interchangeable and, although each have different advantages and disadvantages, they can be considered equivalent. The committee agreed with the company assumption that the standard care arm of KEYNOTE-177 could be used for the clinical efficacy of CAPOX. It concluded that FOLFOX, FOLFIRI and

CAPOX were equally effective.

Cetuximab and panitumumab are equally effective

3.16 The committee recalled that people with RAS wild-type colorectal cancer would have cetuximab or panitumumab in combination with chemotherapy. The committee was aware that previous appraisals in this area had explored the efficacy of cetuximab and panitumumab. The results of a network meta-analysis from NICE's technology appraisal guidance on cetuximab and panitumumab for previously untreated metastatic colorectal cancer suggested that there was no significant difference between cetuximab with FOLFOX and panitumumab with FOLFOX and the clinical lead for the Cancer Drugs Fund believed that they should be considered equivalent. The committee concluded that cetuximab and panitumumab are equally effective.

A network meta-analysis is needed to estimate the relative effectiveness of cetuximab or panitumumab compared with pembrolizumab

3.17 The committee recalled the standard care arm in the KEYNOTE-177 trial included cetuximab, but not panitumumab. It noted that only 12% of participants had cetuximab with FOLFOX or FOLFIRI, and recalled that the trial did not determine RAS status for all participants so treatment may not reflect practice in the NHS. It concluded that an alternative source of evidence would be needed to estimate the relative effectiveness of pembrolizumab compared with cetuximab or panitumumab.

The company's network meta-analysis is appropriate to assess the treatment effect of pembrolizumab compared with panitumumab or cetuximab with FOLFOX or FOLFIRI

3.18 The company used a network meta-analysis to compare progression-free survival and overall survival for pembrolizumab compared with panitumumab with FOLFOX. In its submission, the company stated that, because the hazard plots for pembrolizumab and standard care from

KEYNOTE-177 crossed, proportional hazards could not be assumed. Therefore, a network meta-analysis with constant hazard ratios was not appropriate. Instead, the company fit parametric curves to data from both arms of KEYNOTE-177 to estimate time-varying treatment effects. This generated estimates of the probabilities of progression-free and overall survival at 6, 9, 12, 18 and 24 months from randomisation. The company used pooled data from the KEYNOTE-177 control arm as the common comparator in its network meta-analysis. To compare panitumumab with FOLFOX against standard care, it used the PRIME study. PRIME is an open-label phase 3 trial that enrolled people with metastatic colorectal cancer. The company used the treatment effect from the RAS wild-type subgroup in PRIME to represent the population who would have panitumumab combinations in NHS clinical practice. The committee noted that the comparison with standard care used the whole population from KEYNOTE-177, not the RAS wild-type subgroup, so the results are uncertain. Also, no data were available from PRIME that were specific to the high MSI or DNA MMR-deficient population. Because panitumumab with FOLFOX is only used in people with RAS wild-type colorectal cancer in the NHS, the committee would have preferred to see the RAS wild-type subgroup from KEYNOTE-177 standard care used in the comparison. However, the committee acknowledged that the results of the subgroup analyses suggested that pembrolizumab improves progression-free and overall survival compared with panitumumab plus FOLFOX. The committee recalled that panitumumab and cetuximab combinations were broadly equivalent. It concluded that the company's network meta-analysis was appropriate and pembrolizumab was clinically effective compared with panitumumab or cetuximab with FOLFOX or FOLFIRI.

Cost effectiveness

The company's model is appropriate for decision making

3.19 The company's original submission included 2 models. They were a 3-state partitioned survival model (progression-free, progressed disease and death) and a 5-state semi-Markov model that included additional post-surgery health states (progression-free and progressed disease). At

clarification, the company updated the semi-Markov model to remove the post-surgery states on the ERG's request. This was because under 10% of people had surgery in KEYNOTE-177 and the company had assumed that having surgery did not affect overall and progression-free survival. The company calculated the probability of being in a health state using the progression-free survival, time to progression or post-progression survival from KEYNOTE-177, and applied treatment effects from the network meta-analysis to standard care results for panitumumab with FOLFOX. The model cycle length was 1 week, and the time horizon was 40 years. The ERG highlighted that the partitioned survival model included the overall survival data from KEYNOTE-177. The committee acknowledged that both models submitted by the company appeared broadly consistent but recalled its concern that the overall survival data were likely to be biased. For this reason, it agreed that the company's semi-Markov model was most appropriate for decision making.

Survival extrapolations

A piece-wise approach is appropriate for modelling progression-free survival and time to progression

3.20 Analysis suggested that the hazard rates from KEYNOTE-177 were not constant over time. For this reason, the company used a 2-piece model to extrapolate progression-free survival and time to progression. The 2-piece model used Kaplan–Meier data until week 20, then parametric distributions to extrapolate beyond the trial follow up. This was based on clinical advice and visual inspection. In addition, because the assumption of proportional hazards did not hold for the KEYNOTE-177 trial, the company fitted independent curves to the data. Both the ERG and company's final base cases used the Weibull curve to extrapolate progression-free survival and time to progression after 20 weeks, to account for the increasing hazard in the standard care arm. Clinical experts expected 5% to 10% of people having standard care and 30% to 50% of people having pembrolizumab to be progression-free at 5 years. These estimates aligned with the company's preferred extrapolations. The committee noted that the company's choice of the Weibull curve

was conservative because it predicted that fewer people would be progression-free over the modelled time horizon compared with most other distributions. The company explored different distributions and cut-off points from which to transition from observed to modelled data, but the committee noted that these scenarios had limited impact on the cost-effectiveness results. It concluded that a 2-piece model using the Weibull distribution after 20 weeks is appropriate to extrapolate progression-free survival and time to progression.

The company's use of equal post-progression survival for all comparators is likely conservative, but unlikely to reflect clinical practice

3.21 The company used the post-progression survival extrapolated from KEYNOTE-177 data to calculate the probability of moving from progressed disease to death in the model. Because of the high proportion of people in the standard care arm who had subsequent treatment with checkpoint inhibitors, the company assumed that post-progression survival for all comparators equalled that for pembrolizumab. The ERG explained that this approach was conservative because not all people who had standard care went on to have checkpoint inhibitors, but were modelled to have the post-progression survival benefits of pembrolizumab. Clinical experts were concerned that the company's assumption did not reflect outcomes they expected to see in clinical practice, because people who had pembrolizumab would likely have different outcomes after progression than people who had standard care. This was because people whose condition responded to pembrolizumab could have a prolonged response, which was unlikely with standard care, and was associated with improved overall survival and reduced need for subsequent therapies over a person's lifetime. The committee considered that this disease pathway may be better represented by the pembrolizumab progression-free survival curves, which gradually converge with overall survival curves, reflecting that disease progression is not expected to occur in some long-term survivors. The committee recalled its earlier conclusion that overall survival from KEYNOTE-177 was likely biased because over 50% of the standard care arm had had a subsequent checkpoint inhibitor after progression. It noted that the company had presented analyses that

attempted to adjust for treatment switching. However, the company's assumption of equal post-progression survival for all treatments meant it was unnecessary to use these analyses in the economic modelling. It concluded that the company's use of equal post-progression survival for all comparators is likely to be a conservative assumption that avoids using biased overall survival data, but may not reflect what is seen in clinical practice.

Health related quality of life

The company's utilities are appropriate for decision making with exceptions

3.22 In its base case, the company used utility values derived from the EQ-5D-3L health questionnaires collected in the KEYNOTE-177 clinical trial. The company used utilities based on whether disease had yet to progress or had already progressed in its base-case model. It estimated utility values for pembrolizumab and standard care in the progression-free health state separately and used the utility value from standard care for all comparators. Clinical experts agreed that it was plausible that people taking pembrolizumab would have a higher quality of life than people taking chemotherapy, because pembrolizumab was given as a shorter infusion and needed fewer hospital visits and had fewer adverse events. However, the company also included a disutility for adverse events in the progression-free health state. It calculated the disutility from the difference between the utility for the progression-free health state values for people with and without severe adverse events, which it then adjusted for the duration of adverse events. The ERG disagreed with including a disutility for adverse events, stating that adverse events were double counted. This was because the company's progression-free utility values did not distinguish between people who did and did not have a severe adverse event in KEYNOTE-177. The committee did not necessarily agree with the ERG and noted that adverse events may have been included in the treatment-specific utility values only if they occurred at the time of completing the questionnaire. The committee also recalled that the company did not include rare serious adverse events in its model. Yet, it noted that modelling a disutility for adverse

events had limited impact on the cost-effectiveness results. The committee concluded that the company's use of treatment-specific utilities is appropriate for decision making and including a disutility for adverse events makes, as modelled, little difference to the cost-effectiveness results.

Resource use in the model

Pembrolizumab would be given every 6 weeks in the NHS, but this may underestimate costs and resource use

3.23 The committee understood that the marketing authorisation for pembrolizumab included a 200 mg once every 3 weeks and 400 mg once every 6 weeks regimen. The Cancer Drugs Fund clinical lead confirmed that the 2 dosing regimens would be expected to be equally effective. Clinical experts explained that, in general, clinicians would prefer to give pembrolizumab every 6 weeks, for patient convenience and to limit NHS resource use. Also, they would only need monitoring for liver dysfunction every 6 weeks. However, the committee also heard that clinicians would initially give pembrolizumab every 3 weeks until they confirmed how well a person tolerated it and how the condition responded to treatment (expected to be around 3 to 6 months from starting treatment). The committee noted that the company and ERG's base cases modelled pembrolizumab as being given every 6 weeks; therefore the costs of administration and resource use for pembrolizumab would be higher in clinical practice. The committee concluded that after an initial period of 3-weekly administration, pembrolizumab would be given every 6 weeks, and that the model may underestimate costs and resource use.

It is appropriate to apply a 2-year stopping rule for pembrolizumab

3.24 In the economic model, the company assumed that clinicians would stop treatment with pembrolizumab after 2 years (equating to 35 3-weekly cycles of 200 mg), whether or not a person's condition had progressed. This was in line with the KEYNOTE-177 protocol. However, the ERG noted that the summary of product characteristics for pembrolizumab specified

that pembrolizumab could be used until disease progression or unacceptable toxicity. Clinical experts confirmed that in clinical practice, they would stop treatment with pembrolizumab after a maximum of 35 3-weekly cycles of 200 mg in people who had not progressed. This was to align with the clinical trial evidence and because of the belief that limited benefit would be gained from treatment beyond 2 years. The clinical lead for the Cancer Drugs Fund confirmed that, if a stopping rule were implemented, pembrolizumab would not be funded beyond 2 years. However, because people in KEYNOTE-177 had 200 mg of pembrolizumab every 3 weeks, people in the NHS may not receive the full 35 cycles given in the trial within 2 years, because of 6-weekly administration using the higher dosage (400 mg; see section 3.23). It also heard from patient experts that they had both chosen to stop treatment early, despite continued response and the possibility of up to 1 year's further treatment being available. For people in the KEYNOTE-177 trial who stopped their treatment early because they achieved a complete response, they could have 17 more 3-weekly cycles of pembrolizumab (200 mg) upon progression. However, the company confirmed that retreatment was not included in the licence for pembrolizumab. The committee concluded that it was appropriate to apply a 2-year stopping rule for pembrolizumab (given 3- or 6-weekly).

Costs in the economic model

Costs of standard care in the NHS lie between the company's and ERG's estimates

3.25 The committee recalled that around 70% of people in the KEYNOTE-177 standard care arm had a combination that contained bevacizumab, which is not available in NHS clinical practice (see section 3.10). To account for this, the company replaced the costs of bevacizumab with the costs for cetuximab combinations and assumed they were equal. The ERG was concerned that, unlike bevacizumab, cetuximab is available in the NHS only for people with RAS wild-type disease. One clinical expert estimated that less than half of people with untreated metastatic colorectal cancer with high MSI or DNA MMR deficiency would be expected to have RAS wild-type disease and therefore have cetuximab in clinical practice.

Hence, the ERG believed that the company overestimated the costs for standard care. The ERG's base case assumed that half the costs for standard care in the NHS came from the NHS price for FOLFOX and the other half came from the cost for FOLFIRI. The committee noted that this approach underestimated the true costs in the NHS, as the ERG did not include any costs for cetuximab in its base case. Also, the ERG did not adjust the clinical effectiveness of standard care to account for the worse overall survival with FOLFOX and FOLFIRI compared with bevacizumab or cetuximab. The committee noted that the ERG's assumption was conservative, but that it would have liked to have seen a scenario that included cetuximab in the costs for standard care. The committee also recalled that neither the company nor ERG had included capecitabine or FOLFOXIRI as relevant comparators in the model. However, it noted that the clinical effectiveness results compared with standard care included a blended comparator. It recalled its conclusions about the efficacy of blended comparators and noted that similar assumptions applied to the costs. The committee recalled the clinical experts' description of standard care included a small proportion who would have capecitabine monotherapy, which would have lower costs than FOLFOX or FOLFIRI, and a small proportion who would have FOLFOXIRI, which would have higher costs. The committee concluded that the costs of standard care in the NHS are likely between the company and ERG's estimates but that neither reflect the true costs in the NHS. It agreed that it would consider both the ERGs and the company's scenarios in its decision making.

Cost-effectiveness estimates

Pembrolizumab is cost effective against all comparators

3.26 Because of confidential commercial arrangements for pembrolizumab and comparators, none of the cost-effectiveness results are reported here. The committee agreed that its preferred assumptions to compare pembrolizumab with comparators included:

- the full KEYNOTE-177 population for treatment effect
- a 2-year stopping rule

- treatment effect from KEYNOTE-177 standard care for CAPOX, FOLFIRI and FOLFOX
- treatment effect from the company's network meta-analysis for both panitumumab and cetuximab combination therapy
- different utility values for pembrolizumab compared with current treatments, and a disutility adjustment in the progression-free health state
- administration and consultant visits every 6 weeks.

The committee considered the incremental cost-effectiveness ratio (ICER) for both the ERG and company's base cases for pembrolizumab compared with FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX and capecitabine, which differed only in the approach to costing standard care. The ERG's base case, which used standard care costs from FOLFOX and FOLFIRI, increased the ICER compared with the company's assumption that replaced costs of bevacizumab with costs of cetuximab for 70% of the population. It recalled that the cost of standard care in the NHS was likely between the ERG and company's base cases but noted that all estimates of cost effectiveness for this comparison were less than £20,000 per quality adjusted life year (QALY) gained. For the comparison with panitumumab, the company and ERG base cases used identical assumptions and ICERs were less than £20,000 per QALY gained. The committee recalled that pembrolizumab would initially be given every 3 weeks in the NHS and noted that the company and ERG base cases assumed 6-weekly administration. So, the ICER for pembrolizumab in the NHS would be higher against all comparators but would remain below £20,000 per QALY gained. It concluded that pembrolizumab is a cost-effective use of resources in the NHS against all comparators.

Other factors

Pembrolizumab is a step change for people with metastatic colorectal cancer with high MSI or DNA MMR deficiency, and the model captures all benefits

3.27 The company, clinical experts and patient experts stated pembrolizumab represents a step change in treatment for people with metastatic

colorectal cancer with high MSI or DNA MMR deficiency and that there is high unmet need for this population. The committee recalled that there are currently no targeted treatments specific to colorectal cancer with high MSI or DNA MMR deficiency and that these people have worse outcomes than for microsatellite stable disease. The company and clinical experts explained that treatment with pembrolizumab was less toxic, given less frequently and had a shorter administration then comparators. The committee noted that the treatment is not a chemotherapy and has the potential to be curative in some people, which would transform their quality of life. It concluded that pembrolizumab is a step change for people with metastatic colorectal cancer with high MSI or DNA MMR deficiency, and all benefits are captured in the cost-effectiveness estimates.

The recommendation takes potential equality issues into account

3.28 The committee noted an equality concern around testing for high MSI or DNA MMR-deficient disease. Although routinely funded by NHS England (see section 3.8), local uptake and turnaround times for high MSI or DNA MMR deficiency testing are inconsistent throughout the NHS. Clinical experts raised concerns that some people would not be tested as standard, so would not be able to access pembrolizumab if recommended. The committee considered that all people should have testing for high MSI or DNA MMR deficiency when first diagnosed, in line with NICE's diagnostic guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer. It was reassured by the clinical lead for the Cancer Drugs Fund that, should pembrolizumab be recommended and high MSI or DNA MMR deficiency testing inform treatment decisions, it would become routine and timely throughout the NHS. Clinical experts also noted that the current guidance states that clinicians should not wait for results before starting treatment. This could mean people who needed treatment immediately were starting initially on combination chemotherapy and therefore were no longer eligible for pembrolizumab at first line. The committee considered this but had heard from the clinical lead of the Cancer Drugs Fund that testing should be timely. It was aware that it can only make recommendations within the marketing authorisation and any recommendation to switch treatment from chemotherapy to pembrolizumab was therefore outside of the

committee's remit. The committee concluded that it had considered all equalities issues and its recommendation did not need changes.

Conclusion

Pembrolizumab is recommended for routine commissioning

3.29 The committee agreed that the most plausible ICERs for pembrolizumab compared with all relevant comparators were within what NICE normally considers to be an acceptable use of NHS resources. It therefore concluded that it could recommend pembrolizumab for routine commissioning as an option for untreated metastatic colorectal cancer with high MSI or MMR deficiency.

4 Implementation

4.1 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 fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have had a marketing authorisation and been launched in the UK.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal 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 appraisal document.

4.3 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 metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

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Technical lead

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Accreditation