NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence

Pembrolizumab does not currently have a marketing authorisation in the UK for adjuvant treatment of resected melanoma with high risk of recurrence. Pembrolizumab will be made available for use within the Cancer Drugs Fund only if and when it receives its marketing authorisation for this indication. This is anticipated to be early December 2018.

1 Recommendations

1.1 Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for the adjuvant treatment of melanoma with lymph node involvement in adults who have had complete resection. It is recommended only if the conditions in the managed access agreement for pembrolizumab are followed.

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

There are currently no adjuvant immunotherapies recommended by NICE for people who have melanoma with lymph node involvement who have had complete resection.

Clinical evidence comes from KEYNOTE-054, an ongoing randomised trial. It is likely to improve recurrence-free survival but the size of the benefit is unclear in the long term, because the trial is ongoing. Also, data about overall survival and how long people might live without developing distant metastases is limited. This means that the estimates of cost effectiveness are also very uncertain.

Pembrolizumab has the potential to be cost effective, but more evidence is needed to address the clinical uncertainties. Longer follow-up data from KEYNOTE-054 on how many people develop distant metastases and overall survival would help to address some of the uncertainties. Therefore, pembrolizumab is recommended for use in the Cancer Drugs Fund for people who have melanoma with lymph node involvement who have had complete resection.

2 Information about pembrolizumab

Anticipated marketing authorisation indication	Pembrolizumab (KEYTRUDA, Merck Sharp & Dohme) has an anticipated marketing authorisation as monotherapy for 'the adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection'. On 18 October 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product pembrolizumab. The CHMP adopted a new indication as follows: Keytruda as monotherapy is indicated for the adjuvant treatment of melanoma in adults with lymph node involvement who have undergone complete resection. The exact wording of this indication will be available in the summary of product characteristics when pembrolizumab receives its marketing authorisation.
Dosage in the marketing authorisation	200 mg every 3 weeks by intravenous infusion for 1 year
Price	£2,630.00 per 100 mg vial (excluding VAT; British national formulary [BNF] online [accessed September 2018]). 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 (section 7) considered evidence submitted by Merck, Sharp and Dohme and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical need and current management

People with completely resected stage III melanoma have a high unmet clinical need

3.1 Melanoma has a substantial effect on patients, their carers and the wider society. Five-year survival estimates are about 50% to 55% for stage III disease. People with fully resected stage III melanoma are still at high risk of disease recurrence, with 5-year relapse-free survival of 28% to 44%. The clinical and patient experts emphasised the importance of access to more treatment options, particularly as an adjuvant treatment for people living with melanoma. The clinical expert explained that adjuvant treatment aims to remove any disease after resection to reduce the risk of relapse and progression to metastatic disease. The committee concluded that people with resected stage III melanoma have a high unmet clinical need and would value new treatment options.

Adjuvant treatment will change the treatment pathway for stage III melanoma

3.2 The standard treatment for most people with stage III melanoma is resection of the tumour and associated lymph nodes. The clinical expert explained that surgical practice is changing for patients with stage IIIA disease because recent evidence showed that there is no overall survival benefit in these patients after full resection of the regional lymph nodes. After a full resection, the standard of care is routine surveillance which includes regular clinical review and imaging. The clinical experts explained that adjuvant radiotherapy and immunotherapy after tumour removal are not widely used in UK practice. The committee understood that adjuvant pembrolizumab would be used at this point in the treatment pathway. The clinical expert explained that adjuvant treatment aims to remove any residual microscopic disease after resection to reduce the risk of relapse and progression to incurable metastatic disease. Treatment options for metastatic disease include immunotherapies. The clinical

expert explained that some patients will develop metastatic disease after adjuvant therapy, and if pembrolizumab was used in the adjuvant setting it might affect subsequent immunotherapy treatment options. This is because pembrolizumab is already used to treat metastatic disease after relapse and is unlikely to be used again. The committee concluded that pembrolizumab as adjuvant treatment will change the treatment pathway for stage III melanoma.

Clinical evidence

KEYNOTE-054 is generalisable to clinical practice in England

3.3 Clinical-effectiveness data for pembrolizumab compared with routine surveillance came from KEYNOTE-054, an ongoing randomised trial. This included people with stage IIIA (more than 1 mm lymph node metastasis), stage IIIB and stage IIIC melanoma (using the AJCC 7th Edition staging). All patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and had complete resection. The most common stage was stage IIIB (about 46%), and most had programmed cell death-1 ligand-1 (PD-L1) positive disease (about 84%). The clinical lead for the Cancer Drugs Fund noted that stage III disease is considered high enough risk to consider adjuvant treatment. The clinical expert explained that the overall population in KEYNOTE-054 was likely to be the same as those who would have pembrolizumab as adjuvant treatment in clinical practice because the people who develop melanoma are usually fit with an ECOG score of 0 or 1. The ERG and clinical expert noted that KEYNOTE-054 was a well-designed trial. The committee concluded that the population in KEYNOTE-054 was generalisable to clinical practice in England and suitable for decision-making.

Pembrolizumab improves recurrence-free survival compared with routine surveillance but the size of the benefit in the long term is unclear

3.4 At the most recent data cut (October 2017) of KEYNOTE-054 median recurrence-free survival in the pembrolizumab arm had not been reached. The median follow-up was 16 months (range: 2.5 to 25.3 months).

Table 1 Clinical data from KEYNOTE-054

		Pembrolizumab	Placebo
Number of patients		514	505
Recurrence-free survival, median (95% confidence interval [CI])		Not reached (not estimable to not estimable)	20.4 (16.2 to not estimable)
RFS rate (%) at 6 months		82.2 (78.6 to 85.3)	73.3 (69.2 to 77.0)
RFS rate (%) at 12 months		75.4 (71.3 to 78.9)	61.0 (56.5 to 65.1)
RFS rate (%) at 18 months		71.4 (66.8 to 75.4)	53.2 (47.9 to 58.2)
Hazard ratio (98.4% CI)*		0.57 (0.43 to 0.74); p<0.0001	
Type of first event, n (%)	Loco-regional recurrence	55 (10.7)	77 (15.2)
	Distant metastasis	69 (13.4)	114 (22.6)
	Death	2 (0.4)	1 (0.2)

* Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1 to 3 nodes vs. IIIC ≥4 nodes) as indicated at randomisation.
Abbreviations: RFS – recurrence-free survival; CI – confidence interval

The company calculated a hazard ratio based on a Cox proportional hazards regression model from the recurrence-free survival data from KEYNOTE-054, shown in table 1. Pembrolizumab showed a statistically significant improvement in recurrence-free survival compared with placebo. The ERG was concerned about the methods used to calculate

the hazard ratio because it is unlikely that the proportional hazards assumption would hold. The clinical lead for the Cancer Drugs Fund noted that it is unusual for adjuvant therapies to show such a pronounced recurrence-free survival benefit this early in follow-up, and that the benefit of pembrolizumab as adjuvant treatment compared with placebo is clinically significant. The committee noted that the median duration of follow-up in the trial (16 months) is very short. This made it difficult to know whether pembrolizumab will continue to have a large benefit on recurrence-free survival in the long term. The committee concluded that pembrolizumab improves recurrence-free survival compared with placebo but the size of the benefit in the long term is unclear.

Pembrolizumab may improve overall survival but more data from KEYNOTE-054 is needed

3.5 Overall survival data from the ongoing KEYNOTE-054 trial were not available in the October 2017 data cut. The company noted that recurrence-free survival is a reliable surrogate marker for overall survival based on the conclusions of a meta-analysis by Suciu et al. (2018). This included 13 studies and over 5,000 people. All of the studies included in the meta-analysis were of interferon as adjuvant treatment compared with no interferon in people with surgically resected stage II and III melanoma. The meta-analysis concluded that a hazard ratio of 0.77 or less for recurrence-free survival would predict a treatment benefit on overall survival. However, the ERG cautioned against using surrogate end points to estimate long-term benefit based on this meta-analysis because:

- it was from another treatment (interferon) which is not currently used in the NHS
- it included data that had assumed proportional hazards and that these were unlikely to hold

- the characteristics of people included in the meta-analysis were different from people in the KEYNOTE-054 trial
- the data included in the meta-analysis are from studies that were published before 2008 and that surgical techniques for melanoma have advanced in the last 10 years.

The committee accepted that, based on the promising effect of pembrolizumab on recurrence-free survival, it may improve overall survival compared with routine surveillance. However, the committee concluded that until overall survival data are reported from KEYNOTE-054, the survival benefit with pembrolizumab cannot be confirmed.

Adverse events

Although pembrolizumab is well tolerated, a careful assessment of the likely benefits and adverse events of treatment is important

3.6 KEYNOTE-054 showed that pembrolizumab was generally well tolerated. The clinical expert explained that in clinical practice, particularly compared with ipilimumab and chemotherapy, adverse events can be detected and treated much earlier. The committee noted that the common side effects which happen during treatment are generally manageable. However, immunotherapy (such as pembrolizumab) works by altering the immune system. The clinical expert explained that a small proportion of people develop irreversible disorders, in particular Type 1 diabetes. The clinical experts explained that because some people have a lower risk of relapse after resection, a careful assessment and discussion about the risks and potential benefits of pembrolizumab would be needed. Although pembrolizumab is well tolerated, the committee agreed that a careful assessment of the likely benefits and adverse events of treatment is important.

The company's economic model

The company's model structure is acceptable for decision-making

3.7 The company presented a 4-state transition model to estimate the cost effectiveness of pembrolizumab as an adjuvant treatment compared with routine surveillance. Groups of patients were able to move between the recurrence-free survival, loco-regional recurrence, distant metastases and death health states. The model used data on first recurrence events from KEYNOTE-054 to inform model transitions from the recurrence-free survival health state to loco-regional recurrence and distant metastases health states and from recurrence-free survival and loco-regional recurrence to death. Transitions from loco-regional recurrence to distant metastases were based on data from the Flatiron database, an electronic health records database used in the United States. Data from KEYNOTE-006, a randomised trial comparing pembrolizumab with ipilimumab in people with unresectable or advanced melanoma, and a network meta-analysis done by the company were used to inform transitions from distant metastases to death. The ERG was satisfied that the model structure was suitable for estimating the cost effectiveness of pembrolizumab compared with routine surveillance. The committee concluded that the model structure is acceptable.

More data on distant metastases-free survival is needed

3.8 Data on distant metastases-free survival from KEYNOTE-054 are incomplete because the trial is still ongoing (see section 3.3). Therefore the company's modelled estimates of distant metastases-free survival are based on immature data. The company validated their modelled estimates in the routine surveillance arm by comparing the distant metastases-free survival estimate at 5-years with that in the routine surveillance arm of EORTC 18071, a trial of ipilimumab as an adjuvant treatment. The company's estimate of 5-year distant metastases-free survival for routine

surveillance was lower than EORTC 18071 (30.2% in company model compared with 38.9% in EORTC 18071). The ERG also highlighted that the company's model estimated 91.6% of all people on routine surveillance develop distant metastases after 46 years. This suggested that almost no-one with completely resected stage III disease would stay disease free and the committee and ERG considered this implausible. The committee considered that the distant metastases-free survival estimates from the company's model for routine surveillance are unreliable given the data available. The committee concluded that more data on distant metastases-free survival from the ongoing KEYNOTE-054 trial should reduce uncertainty in the modelling.

More mature data on overall survival is needed

3.9 Data on overall survival from KEYNOTE-054 are incomplete and full data are not yet available because the trial is still ongoing (see sections 3.3 and 3.5).Data from KEYNOTE-006 and a network meta-analyses of treatments for advanced melanoma were used to inform transitions from distant metastases to death in the model (see section 3.7). To extrapolate overall survival for pembrolizumab, an exponential curve was fitted to individual patient data from KEYNOTE-006. The company then used the results of a network meta-analyses of treatments for advanced melanoma and applied a hazard ratio for the effectiveness of the subsequent treatment to the overall survival for pembrolizumab. The committee noted that this method relies on proportional hazards and this assumption may not hold (see section 3.4) so the method may not be appropriate. The committee was aware that the company validated their model's projections for overall survival in routine surveillance by comparing their estimate at 5-years against those in the routine surveillance arm of EORTC 18071. The ERG did a further validation of the company's model. It created a composite stage III survival curve using overall survival data from the 2010 Surveillance, Epidemiology, and End Results Program

(SEER) database for patients with stage III melanoma by AJCC 7th Edition, weighted by the proportion of patients in each of these stages in KEYNOTE-054. The composite overall survival curve approximated the expected overall survival for the routine surveillance arm of KEYNOTE-054. The ERG was concerned that overall survival in the company's model produces clinically implausible estimates. This is because in the first 5-years, the projected overall survival in the routine surveillance arm of the company's model is higher than the ERG's composite expected overall survival curve. After 5 years, the company's modelled overall survival is lower than the overall survival estimated from the ERG's composite curve. By year 10, the company's model projected overall survival curve for routine surveillance is about the same as the 2010 SEER overall survival curve for patients with stage IIIC disease. The committee noted that there was very limited overall survival data from KEYNOTE-054 and concluded that it is not possible to resolve the uncertainty in the model predictions until more mature data are available.

Duration of treatment effect with pembrolizumab is uncertain

3.10 The company assumed a lifetime treatment benefit for pembrolizumab after stopping treatment. They presented 2 scenarios in which this assumption was tested. A clinical expert reported in their written statement that the duration of treatment benefit with pembrolizumab as an adjuvant treatment is unknown. The ERG noted that the data are too immature to assess if there is a lifetime treatment benefit associated with pembrolizumab as an adjuvant treatment. It highlighted that the model outcome is sensitive to the duration of treatment benefit and shortening this with pembrolizumab from lifetime (46 years) to 3 years results in pembrolizumab as adjuvant treatment being cost incurring over the model time horizon, rather than being cost-saving. The company noted that more mature data from later data-cuts of the ongoing KEYNOTE-054 trial will help resolve this uncertainty. The committee recognised the uncertainty in

the assumption of lifetime treatment benefit with pembrolizumab as adjuvant treatment and concluded that more mature data on overall survival would help decision-making.

The company's assumptions about subsequent treatments are not appropriate

3.11 The company used market share data to estimate the proportion of people having treatment for metastatic disease. The clinical lead for the Cancer Drugs Fund noted that the market share data used by the company did not reflect the use of these treatments in the NHS, for example vemurafenib is rarely used. However, the ERG explained that the treatments for advanced melanoma do not have much effect on the outcome of the company's model. This is because over the model time horizon, the proportion of patients with distant metastases who go on to have subsequent therapies is about the same between the pembrolizumab and routine surveillance arms. The committee recalled that the data used to model the transitions to distant metastases are immature and the company's model predictions are uncertain (see section 3.8). The committee concluded that although the model results are not sensitive to this assumption, the market share data used in the company's model for subsequent therapies does not reflect clinical practice.

Pembrolizumab is not recommended for routine use in the NHS

3.12 The committee considered the incremental cost-effectiveness ratios (ICERs) presented by the company which included the commercial arrangement for pembrolizumab. The ERG also incorporated the commercial arrangements for the subsequent treatments given to people who develop metastatic disease. The exact ICERs cannot be reported because the commercial arrangements are confidential. The results showed that in the company's base case and scenario analyses, the ICERs for pembrolizumab compared with routine surveillance did not

exceed £10,000 per quality-adjusted life year (QALY) gained in any of the analyses. They explored:

- a shorter model time horizon (10 years)
- different parametric models to estimate transitions from the recurrence-free survival health state
- different assumptions for the treatment benefit duration with pembrolizumab
- including PD-1 inhibitors for the treatment of metastatic disease.

The committee noted that the company's ICERs were within the range usually considered a cost-effective use of NHS resources. The ERG did not do any exploratory analyses because the data from KEYNOTE-054 were too immature and noted that only 1% of the total discounted QALYs came from the actual trial data. Considering the very limited data for distant metastases-free and overall survival, the committee agreed the ICER for pembrolizumab compared with routine surveillance was very uncertain. Therefore, the committee concluded the ICER for pembrolizumab compared with routine surveillance was very uncertain, and as this is a significant change to the existing treatment pathway for melanoma, it could not recommend pembrolizumab for routine use.

Cancer Drugs Fund

The committee considered pembrolizumab as an option for use in the Cancer Drugs Fund

3.13 Having concluded that pembrolizumab could not be recommended for routine use, the committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee noted that the company's ICERs were within the range usually considered a cost-effective use of NHS resources (see section 3.12). Although the

committee was concerned that the ICERs were very uncertain. It noted that the results reported in the KEYNOTE-054 trial were promising and showed that pembrolizumab does improve recurrence-free survival compared with placebo. Also, until overall survival is reported in KEYNOTE-054, an overall survival benefit with pembrolizumab has not yet been shown. The committee was aware that KEYNOTE-054 is ongoing and that further data will become available for:

- recurrence-free survival
- distant metastases-free survival
- overall survival.

The committee understood that more data from KEYNOTE-054 would also help to assess the validity of the proportional hazards assumption (see section 3.4); estimate the duration of treatment effect with pembrolizumab (see section 3.10) and help address the uncertainty around the re-use of pembrolizumab to treat metastatic disease after use in the adjuvant setting (see section 3.2).The committee discussed whether there was potential for pembrolizumab to be cost effective. It recalled its conclusion that the current cost-effectiveness results were very uncertain, but given the clinical benefit and range of ICERs presented to the committee, it agreed that pembrolizumab has the potential to be cost effective compared with routine surveillance. The committee concluded that pembrolizumab met the criteria for inclusion in the Cancer Drugs Fund. It recommended pembrolizumab for use within the Cancer Drugs Fund as an option for people with melanoma with lymph node involvement who have had complete resection if the conditions in the managed access agreement are followed.

Innovation

Pembrolizumab's benefits are captured in the measurement of QALYs

3.14 The company considered pembrolizumab to be an innovative treatment. The patient organisation expert and clinical expert explained that there is an unmet need for adjuvant treatment. The committee heard that pembrolizumab has the potential to prevent people developing metastatic disease. The committee concluded that pembrolizumab would be beneficial for patients, but that it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has melanoma with lymph node involvement who have had complete resection 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 and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it

within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

5 Recommendations for data collection

5.1 Proposals for further data collection in the Cancer Drugs Fund include:

- recurrence-free survival
- distant metastases-free survival
- overall survival
- long-term follow-up of people who received pembrolizumab as an adjuvant treatment who develop advanced disease and receive pembrolizumab again to treat metastatic disease.

6 Review of guidance

6.1 The data collection period is expected to end when sufficient data has been collected to address the committee's uncertainties. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

6.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in NICE's Cancer Drugs Fund methods guide (addendum).

Dr Jane Adam
Chair, Appraisal Committee
September 2018

7 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 A.

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.

Emily Eaton Turner
Technical Lead

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