

Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma

Technology appraisal guidance

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www.nice.org.uk/guidance/ta766

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 are 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.

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.

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This guidance replaces TA553.

1 Recommendations

- 1.1 Pembrolizumab is recommended, within its marketing authorisation, as an option for the adjuvant treatment of completely resected stage 3 melanoma with lymph node involvement in adults. It is recommended only if the company provides pembrolizumab according to the [commercial arrangement](#).

Why the committee made this recommendation

Until recently, standard care for people with completely resected melanoma was routine surveillance. Adjuvant treatments such as nivolumab are now available for some people.

Clinical evidence shows that adjuvant pembrolizumab increases how long people live without the cancer coming back compared with placebo. There is still not enough data to know how much pembrolizumab increases how long people live.

Because of this uncertainty the cost-effectiveness estimates vary. However, the most likely estimates are within what NICE considers an acceptable use of NHS resources. Therefore, pembrolizumab is recommended.

2 Information about pembrolizumab

Marketing authorisation indication

- 2.1 Pembrolizumab (Keytruda, MSD) is indicated 'for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection'.

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 £2,630.00 per 100 mg/4 ml concentrate for solution for infusion vial (excluding VAT; BNF online, accessed November 2021). 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 MSD, 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.

Clinical pathway

Pembrolizumab is a highly valued treatment option for people with melanoma

- 3.1 Melanoma often affects people at a younger age than some other cancers. It has a substantial effect on people and their families and carers. Tumour and associated lymph node resections are standard treatment for most people with stage 3 melanoma. Until recently, standard care for people with completely resected melanoma was routine surveillance. In 2018, [NICE's technology appraisal guidance on dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma](#) recommended it for use. In 2021, [NICE's technology appraisal guidance on nivolumab for adjuvant treatment of completely resected melanoma](#) recommended it for use. Nivolumab and pembrolizumab have the same mechanism of action because both are checkpoint inhibitors (PD-1 inhibitors). However, pembrolizumab can be administered every 6 weeks, whereas nivolumab is administered every 4 weeks. Clinical experts stated that about 80% of people have adjuvant pembrolizumab and 20% have nivolumab. They noted that nivolumab has a wider licence, because it is also available for adjuvant treatment of completely resected metastatic melanoma (that is, stage 4 melanoma). However, because of its reduced administration schedule, many patients and NHS services prefer pembrolizumab. This is because it means less time having infusions, and travelling for treatment less frequently. In the previous appraisal of pembrolizumab, NICE recommended it for use within the Cancer Drugs Fund for the adjuvant treatment of stage 3 melanoma with lymph node involvement in adults who have had complete resection (NICE technology appraisal guidance 553, from now TA553). The aim of adjuvant treatment is to remove any residual microscopic disease after resection to reduce the risk of relapse and progression to metastatic disease, which is currently considered incurable. The clinical experts explained that treatments that can be given very early (in the

adjuvant setting) are expected to reduce the number of people returning with metastatic disease. The committee heard from the patient expert that the availability of pembrolizumab through the Cancer Drugs Fund had been life changing for many people with melanoma. The committee concluded that pembrolizumab was a highly valued adjuvant treatment option for people with stage 3 melanoma.

Clinical evidence

Pembrolizumab improves recurrence-free survival and distant metastases-free survival compared with placebo, but overall survival data is immature

3.2 KEYNOTE-054 is an ongoing multinational randomised double-blind trial. It compared adjuvant pembrolizumab with placebo in 1,019 adults who have had complete resection of stage 3 melanoma. The median age of people who had pembrolizumab was 53.9 years. Of the people with known BRAF status who had pembrolizumab, just over half had melanoma with mutations in the BRAF gene (244/478; 51%). In TA553, people in KEYNOTE-054 were followed for a median duration of 16 months. A statistically significant improvement in recurrence-free survival was seen with pembrolizumab compared with placebo (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.43 to 0.74). Both distant metastases-free survival data and overall survival data were immature. Since TA553, people in KEYNOTE-054 have been followed for a median duration of 45.5 months. A statistically significant improvement in recurrence-free survival was seen with pembrolizumab compared with placebo (HR 0.59, 95% CI 0.49 to 0.70). A statistically significant improvement in distant metastases-free survival was seen with pembrolizumab compared with placebo (HR 0.60, 95% CI 0.49 to 0.73). Overall survival data was still immature. Through the Cancer Drugs Fund, systemic anti-cancer therapy (SACT) data was collected from people having adjuvant pembrolizumab for resected stage 3 melanoma. Between 19 November 2018 and 18 November 2020, 1,324 people had adjuvant pembrolizumab, with a median age of 64 years. Most people (81%) had disease without mutations in the BRAF gene. Most people had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 (69%). Compared with KEYNOTE-054, people were older, fewer had mutations in the BRAF gene and fewer had an ECOG score of 0. At the end of the data collection period, 47% of people were still having treatment. The estimate of median overall survival

was not reached. The committee concluded that pembrolizumab improves recurrence-free survival and distant metastases-free survival compared with placebo, but overall survival data is still immature.

It is likely that improvements in recurrence-free and distant metastases-free survival are associated with an overall survival benefit

3.3 The committee was aware that there were challenges in gathering and interpreting overall survival data for adjuvant therapies, such as pembrolizumab for melanoma. This is because people have no known disease at the time of treatment. Instead, treatment is used as a precaution to make sure there is no remaining microscopic disease, and to minimise the risk of recurrence (see [section 3.1](#)). This means that some people having adjuvant treatment would not have gone on to develop advanced disease. People may live for a long time because adjuvant treatment is given in the earlier stages of cancer. However, this means that collecting sufficient data may take a long time. So, it is difficult to know whether adjuvant treatment permanently cures disease or just delays progression. The committee noted that a key reason for recommending pembrolizumab within the Cancer Drugs Fund in TA553 was to get more mature overall survival data. However, data remained immature after exit from the Cancer Drugs Fund. This is because there were too few deaths to estimate accurately the average time that people survive when having pembrolizumab or placebo. In the absence of overall survival data, the committee considered whether recurrence-free or distant metastases-free survival could be used as a surrogate for overall survival. The clinical experts explained that if a treatment makes a clinically meaningful difference to distant metastases-free survival then it was likely that this would be reflected in overall survival. The committee agreed that this was biologically plausible. The patient and clinical experts also advised that, for people with melanoma, overall survival was not their sole focus. Length of time without disease recurrence was also very important. Therefore, recurrence-free and distant metastases-free survival are important outcomes for people regardless of their likely associated improvement in overall survival. The committee concluded that, based on its earlier conclusion that pembrolizumab improved recurrence-free survival and distant metastases-free survival compared with placebo, it was likely that pembrolizumab also improved overall survival benefit. However, given the immaturity of overall survival data, the level of this benefit is uncertain.

Although the data on subsequent treatments is still immature, the data from the SACT cohort reflects clinical practice

3.4 A number of therapies are available if the cancer comes back after adjuvant pembrolizumab (see [NICE's webpage on skin cancer](#)). These include immunotherapies (nivolumab with ipilimumab, nivolumab monotherapy, pembrolizumab monotherapy and ipilimumab monotherapy), and targeted therapy for melanoma with mutations in the BRAF gene (encorafenib with binimetinib, dabrafenib with trametinib, dabrafenib monotherapy and vemurafenib monotherapy). According to the company, further data on subsequent treatments collected from KEYNOTE-054 was incomplete with respect to combination regimens and so did not reflect UK clinical practice. The evidence from the Cancer Drugs Fund after use of adjuvant pembrolizumab is limited, and so far only 12% of people have had subsequent treatments. Most people had nivolumab with ipilimumab (54.2%), ipilimumab (19%), dabrafenib with trametinib (13.7%) and encorafenib with binimetinib (8.5%). Because the data is immature, it is based on cancer that relapsed early, so may not be representative of all completely resected stage 3 melanoma. The clinical experts stated that the immaturity of the data is a positive aspect, because it suggests that the number of people whose disease comes back after adjuvant pembrolizumab is low. The committee was aware that the choice of subsequent treatment will depend on many factors. Most people who can tolerate a combination therapy would be offered nivolumab with ipilimumab after both routine surveillance and adjuvant pembrolizumab. People who cannot tolerate a combination therapy may be offered monotherapy. The choice of immunotherapy is likely to depend on whether adjuvant pembrolizumab was given and, if it was, on the time since the last dose. People with melanoma with mutations in the BRAF gene may choose targeted therapies because they are less toxic and can be taken orally (immunotherapy is given by intravenous infusion). Clinicians agreed that the subsequent treatments seen in the SACT cohort are consistent with what would be expected in clinical practice. Because the trial data was incomplete and therefore deemed to not reflect clinical practice, they considered there was a greater degree of certainty with data from the Cancer Drugs Fund. The committee concluded that subsequent treatment data is still immature but that data from the Cancer Drugs Fund reflects clinical practice.

Adverse events

Although pembrolizumab is well tolerated, it is important to carefully assess the likely benefits and adverse events of treatment

3.5 The committee had previously noted in TA553 that for people taking immunotherapies such as pembrolizumab, a small proportion have irreversible side effects like type 1 diabetes. The committee further heard that, although 80% of people have no toxicity associated with pembrolizumab, and 10% have low impact events, around 5% to 10% have high toxicity. This is frequently in the liver and bowel and needs immune suppression. A further group of people, though extremely small, are at risk of extreme toxicity. This includes immune-mediated damage to the heart, or toxicity on the endocrine system associated with long-term effects. The clinical experts explained that toxicity associated with the endocrine system does not resolve. Also, for people who do experience toxicity, it can take a lot of immune suppression to get the immune system back under control. This is partially because of the long half-lives of pembrolizumab and nivolumab. For these reasons, the clinical experts noted that it was important for patients to weigh up the risks and benefits when considering adjuvant treatment. The experts also stated that people who experience toxicity may in some cases have better outcomes, because it is an indication that their immune system has been activated. The committee concluded that although pembrolizumab is well tolerated, 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

3.6 Overall survival data is a requisite input for a partitioned survival model. In the absence of this, 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 updated data on recurrence-free survival from KEYNOTE-054 to inform model transitions from the recurrence-free survival health state. The model used the distant metastases-free survival data

now available to inform transition from the recurrence-free and loco-regional recurrence health states. A network meta-analysis done by the company was 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.

Survival modelling in the economic model

Estimates of overall survival are highly uncertain despite the additional analyses the company provided

3.7 As in TA553, overall survival data from KEYNOTE-054 is not yet available because the trial is still ongoing. Despite not being in the model as a health state, overall survival is an output of the company's model. The ERG raised concerns that the modelled overall survival outputs for both pembrolizumab (likely overestimated) and routine surveillance (likely underestimated) were unreliable. The company accepted that its estimates were associated with uncertainty. It therefore attempted to explore this uncertainty by comparing its modelled estimates of overall survival with other validation sources (see [section 3.8](#) and [section 3.9](#)). It also explored the effect on cost-effectiveness results of using other combinations of parametric curves fitted to the data (see [section 3.10](#)).

The company explored alternative data validation sources for overall survival for routine surveillance, but all are uncertain

3.8 Because of the uncertainty associated with the survival data in its model, the company used a number of sources to validate the data it had used. For its modelled overall survival outputs for routine surveillance, the company compared it with:

- the placebo arm from the COMBI-AD trial (a randomised controlled trial [RCT] comparing adjuvant dabrafenib plus trametinib with matched placebos for resected stage 3 melanoma with a BRAF V600 mutation)
- the composite curve produced by the ERG during TA553

- the placebo arm from EORTC-18071 (an RCT comparing adjuvant ipilimumab with placebo for completely resected high-risk stage 3 melanoma)
- data from the American Joint Committee on Cancer's (AJCC) 8th edition of melanoma staging
- data from the surveillance epidemiology and end results (SEER) database in the US
- projections taken from TA553.

The company preferred the composite curve produced by the ERG during TA553. The ERG noted that this was based on SEER data published in 2010. It advised that significant gains in overall survival have been achieved since then, after the introduction of immunotherapies and targeted therapies. The committee noted that the SEER database was based in the US, so it was not sure if data would be generalisable to the NHS. The ERG's preferred validation measure was AJCC. Clinical experts stated that there is concern that this data is overly optimistic because it comes from 10 large academic centres and is not population-based registry data. They noted that 3 major publications report worse outcomes for people with stage 3 melanoma than those reported by the AJCC. The committee concluded that the data validation sources for routine surveillance were uncertain, and it would take this uncertainty into account in its decision making.

The company explored alternative data validation sources for overall survival for pembrolizumab, but all are uncertain

3.9 Because of the uncertainty associated with the survival data in its model, the company used a number of sources to validate the data it had used. For its modelled overall survival outputs for pembrolizumab, the company compared it with:

- the nivolumab arm from CheckMate 238 (an RCT comparing adjuvant nivolumab with ipilimumab in resected stage 3B to 3C and stage 4 melanoma)
- pembrolizumab data from the SACT dataset provided by Public Health England; this was the validation measure preferred by the ER
- the ipilimumab arm from EORTC-18071 (described in [section 3.8](#))
- projections taken from TA553

- KEYNOTE-053/SWOG-S1404 (an RCT comparing adjuvant pembrolizumab with high-dose interferon in high-risk resected melanoma).

The committee noted that the population in the SACT dataset (the ERG's preferred source) were older and fewer people had an ECOG score of 0. Also, fewer people had a BRAF mutation (which clinical experts reported generally indicates a higher probability of the cancer responding to treatment) compared with KEYNOTE-054. There is uncertainty around the company's preferred validation measures, the nivolumab arm from CheckMate 238 and the pembrolizumab arm from KEYNOTE-053/SWOG-S1404. The committee was willing to accept that these showed an overall survival benefit for these treatments, but the extent of this benefit was uncertain. The committee concluded that the data validation sources for pembrolizumab were uncertain, and that it would take this uncertainty into account in its decision making.

The company explored alternative extrapolation curves for overall survival, but all are uncertain

- 3.10 The company explored alternative parametric extrapolation curves by either improving survival for the routine surveillance arm, worsening survival in the pembrolizumab arm, or both simultaneously. However, both the ERG and the committee noted that these curves lacked a clear justification for their selection. The ERG stated that the alternative curves did not add value because the additional overall survival did not appear until about 10 years. Because KEYNOTE-054 has yet to report data on overall survival, the ERG stated that the parametric curves should show a difference in overall survival between 0 and 5 years to be considered valid. Such a difference would then be consistent with the lack of overall survival data from KEYNOTE-054. The company agreed the model was probably underestimating overall survival. But it was confident that the modelled overall survival output for its pembrolizumab arm was accurate, because it closely matched data provided from a trial in a similar population, KEYNOTE-053 (see [section 3.9](#)). The ERG stated that if this were true (that is, if the model was overestimating deaths but the modelled estimated deaths in the pembrolizumab arm were accurate), then this overestimation of deaths must be solely driven by an overestimation of deaths in the routine surveillance arm. If true, this would bias the cost-effectiveness results in favour of pembrolizumab. The committee concluded that the extrapolation of overall survival was uncertain.

Cost-effectiveness results

The cost-effectiveness estimates are uncertain

3.11 The committee considered the revised cost-effectiveness estimates submitted by the company. These included the confidential patient access schemes for pembrolizumab but did not include the patient access schemes for subsequent treatments. The company presented a range of incremental cost-effectiveness ratios (ICERs) that explored different assumptions. These included fitting different parametric curves to the recurrence-free and distant metastases-free survival data from the trial (see [section 3.5](#)). It also presented several other scenarios with different time horizons, different sources for subsequent treatment market shares and different utilities. The company's deterministic base case resulted in an ICER of £9,357 per quality-adjusted life year (QALY) gained. Its probabilistic base case gave an ICER of £10,378 per QALY gained. The ICER that was considered the most conservative in the range presented by the company was the scenario that used more pessimistic projections for pembrolizumab overall survival and more optimistic projections for routine surveillance overall survival. This resulted in an ICER of £26,493 per QALY gained. Because of the uncertainty in overall survival, the ERG did not consider any of the company's ICERs to be plausible. However, the ERG did not do any additional analyses to quantify this uncertainty, stating that it was not possible for it to produce more reliable estimates than what the company had produced. The committee agreed that there was uncertainty around overall survival (see [section 3.5](#)). But it concluded that the highest plausible ICER, which could be considered the most conservative, was £26,493 per QALY gained. This did not include the discounts for subsequent treatments used in the model.

The most likely estimate is within what NICE considers a cost-effective use of NHS resources

3.12 When the committee took into account all the confidential patient access schemes for subsequent treatments, all of the resulting ICERs were less than £30,000 per QALY gained. However, these were all associated with uncertainty. The committee would have preferred that the company and ERG had more robustly explored this uncertainty. However, any remaining uncertainty could be mitigated by the fact that nivolumab is recommended in [NICE's technology appraisal guidance on nivolumab for adjuvant treatment of completely resected](#)

melanoma with lymph node involvement or metastatic disease. Nivolumab has a similar mechanism of action to pembrolizumab and was found to be cost effective. Also, unlike nivolumab, pembrolizumab is administered every 6 weeks rather than every 4 weeks. This dosing schedule is preferable for many patients and healthcare services (see [section 3.1](#)). Because appointments are further apart, the committee found it likely that pembrolizumab would have reduced administration costs compared with nivolumab, therefore reducing pressure on the NHS. Taking everything into account, the committee concluded pembrolizumab was a cost-effective use of NHS resources.

Conclusion

Pembrolizumab is recommended for routine use

- 3.13 The committee concluded that the most plausible cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. Therefore, pembrolizumab is recommended for the adjuvant treatment of completely resected stage 3 melanoma with lymph node involvement in adults.

4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal 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 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 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 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.
- 4.4 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 completely resected stage 3 melanoma with lymph node involvement 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 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.

Jeremy Dietz

Technical lead

Carl Prescott

Technical adviser

Thomas Feist

Project manager

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Accreditation

