NICE National Institute for Health and Care Excellence

NICE guidance

# Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma

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 Nivolumab with fluoropyrimidine-based and platinum-based combination chemotherapy is recommended as an option for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma in adults whose tumours express PD-L1 at a level of 1% or more. It is recommended only if:

- pembrolizumab plus chemotherapy is not suitable
- the company provides nivolumab according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with nivolumab 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**

Standard care for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma is fluoropyrimidine-based and platinum-based chemotherapy (chemotherapy). Some people may have pembrolizumab plus chemotherapy if their tumours express PD-L1 with a combined positive score (CPS) of 10 or more.

Clinical trial evidence shows that for people whose tumours express PD-L1 at a level of 1% or more, nivolumab plus chemotherapy increases how long they live compared with chemotherapy alone. It also increases the time before their cancer gets worse. Nivolumab plus chemotherapy has only been indirectly compared with pembrolizumab plus chemotherapy. Uncertainty in this comparison means it is difficult to determine which combination is more effective. The cost-effectiveness estimates for nivolumab compared with pembrolizumab are also uncertain, but nivolumab is unlikely to be cost effective compared with pembrolizumab.

When compared with chemotherapy alone, nivolumab plus chemotherapy meets NICE's criteria to be a life-extending treatment at the end of life. Taking this into account, the

cost-effectiveness estimates are likely within what NICE considers an acceptable use of NHS resources for this group. Therefore, nivolumab plus chemotherapy is recommended when pembrolizumab plus chemotherapy is unsuitable.

Tests for suitability of nivolumab (tumours express PD-L1 at 1% or more) or pembrolizumab (tumours express PD-L1 with CPS of 10 or more) should be done at the same time. This is to minimise any unnecessary delays in accessing treatment.

# 2 Information about nivolumab

## Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol Myers Squibb) 'in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression $\geq$ 1%'.

## Dosage in the marketing authorisation

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

## Price

2.3 The list price is £1,097 for a 100-mg vial (excluding VAT; BNF online accessed September 2022). The company has a commercial arrangement. This makes nivolumab 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 Bristol Myers Squibb, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

## The condition

### Oesophageal cancer is often diagnosed late and has a large impact on quality of life and a poor prognosis

3.1 The patient experts explained that there are no screening tools to identify oesophageal squamous cell carcinoma and often the condition is diagnosed at an advanced stage. They explained that people with the condition can struggle to maintain their fitness and manage their condition. The patient experts described that the condition and treatment side effects massively affect patients' quality of life, social experience and relationships with family and carers. They highlighted that advanced oesophageal squamous cell carcinoma is less survivable than other cancers.

## Treatment pathway

### People would welcome a new treatment option for oesophageal squamous cell carcinoma

3.2 NICE's technology appraisal guidance recommends pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737) in adults whose tumours express PD-L1 with a combined positive score (CPS) of 10 or more. The clinical experts explained that pembrolizumab plus chemotherapy is widely used when it is suitable. However, patient experts were aware that some people do not have pembrolizumab plus chemotherapy despite its suitability. The clinical and patient experts

agreed there is an unmet need in people for whom treatment with pembrolizumab plus chemotherapy is not suitable. The clinical experts explained that clinicians would value an additional treatment option because there may be circumstances in which nivolumab is preferred over pembrolizumab. The committee concluded that patients and clinicians would welcome a new treatment for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.

## Testing for suitability of nivolumab or pembrolizumab should be done concurrently in NHS practice

3.3 Suitability of nivolumab and pembrolizumab is assessed by measuring PD-L1 status. The way that PD-L1 positivity was measured and defined differed in the marketing authorisations for nivolumab and pembrolizumab. In the CheckMate-648 trial around half of participants in the intention-to-treat (ITT) population had tumour cell PD-L1 expression with a level of 1% or more in line with nivolumab's marketing authorisation (measure of PD-L1 expression on tumour cells as a ratio percentage). Pembrolizumab was also a suitable option for more than half of these participants because their tumours expressed PD-L1 with a CPS of 10 or more, in line with its marketing authorisation (measure of PD-L1 expression on tumour cells and immune cells as a ratio score). This means that both nivolumab and pembrolizumab were suitable for some people. In the pembrolizumab clinical trial (KEYNOTE-590), 51% of people had tumours that expressed PD-L1 with a CPS of 10 or more. PD-L1 status defined by tumour cell expression was not reported. The clinical experts highlighted that there is no clear clinical justification for attributing each specific test to either nivolumab or pembrolizumab. The committee acknowledged the overlap and differences between the 2 tests and the complexity it introduces. The company explained that, in clinical practice, treatment decisions for oesophageal squamous cell carcinoma might vary at different hospitals. It also explained they will not be based on tumour cell expression and CPS collectively because the 2 tests for assessing PD-L1 are independent of each other. The committee was aware that testing is time and resource intensive. The clinical experts explained that it was preferrable that the 2 tests (tumour cell expression and CPS) would be done concurrently, rather than

sequentially, to determine whether nivolumab or pembrolizumab is suitable and permissible. However, they highlighted that treatment decisions are often guided by local health service protocols which may use different approaches. The clinical experts did not agree on whether sequential testing would occur in practice. Clinical experts noted that testing tumour cell PD-L1 expression may be more accessible to clinicians than testing PD-L1 expression through CPS. This is because most hospitals can do the tumour cell test but few hospitals have facilities to do the CPS test. This means CPS test results can take 2 weeks or more when external testing is needed. Clinical experts suggested that because tumour cell testing is more accessible than CPS testing, clinicians are more likely to request it first when testing sequentially. The clinical and patient experts were concerned that the waiting time for CPS results and requirement for concurrent testing for nivolumab and pembrolizumab suitability could delay starting a suitable immunotherapy. They highlighted that a delay could disadvantage people, because it is better to start treatment as soon as possible so that the immune response associated with immunotherapies is generated as early as possible. There was uncertainty on whether both tests would be done sequentially or concurrently. The committee heard that in clinical practice there were implementation issues for pembrolizumab (TA737; see section 3.4). However, the committee's remit is to compare the clinical and cost effectiveness of new interventions with currently available treatments for the same indication. This is to ensure patients and the NHS access the most effective, best value treatments. So, the committee's evaluation of nivolumab should include a NICE-recommended cost-effective comparator treatment which was available and used in NHS practice such as pembrolizumab. However, the committee noted the implementation issues for pembrolizumab and strongly concluded that tests for pembrolizumab and nivolumab suitability should be done concurrently. This is to minimise unnecessary delays in accessing treatment.

## Chemotherapy and pembrolizumab plus chemotherapy are relevant comparators, subject to the suitability of pembrolizumab

3.4 The company maintained that pembrolizumab plus chemotherapy was recommended too recently to be considered standard of care. It

considered chemotherapy to be the main comparator for nivolumab plus chemotherapy. The clinical experts mentioned that in their centres they had observed slower uptake of pembrolizumab than anticipated. They attributed this to testing capacity issues associated with the COVID-19 pandemic and differences in how diagnostic services do CPS tests. The Cancer Drugs Fund (CDF) lead stated that use of pembrolizumab plus chemotherapy had been increasing slowly, which is not unusual when there is a test needed for treatment. Despite differing opinions on the uptake of pembrolizumab, the clinical experts and CDF lead agreed that pembrolizumab should be considered as a comparator in this appraisal. The committee concluded that:

- chemotherapy alone is a relevant comparator when only nivolumab is suitable (tumour cell PD-L1 expression at a level of 1% or more and a CPS of less than 10)
- pembrolizumab plus chemotherapy is a relevant comparator when both nivolumab and pembrolizumab are suitable options (PD-L1 positivity with tumour cell expression at a level of 1% or more and a CPS of 10 or more).

# Clinical evidence

## CheckMate 648 data for the subgroup of people whose tumour cells express PD-L1 at 1% or more is appropriate for decision making

3.5 CheckMate 648 is a randomised, three-arm, open-label, placebo-controlled trial (n=970). It compared cisplatin and fluorouracil, with or without nivolumab, and nivolumab plus ipilimumab, as first-line treatment for unresectable advanced, recurrent or metastatic oesophageal cancer. The nivolumab plus ipilimumab and chemotherapy trial arm was not included in the decision problem. The primary outcomes were progression-free survival and overall survival in the ITT population (n=645 for the nivolumab plus chemotherapy and chemotherapy trial arms). Progression-free survival and overall survival were reported for people with squamous cell oesophageal carcinoma whose tumour cells expressed PD-L1 at 1% or more (n=315). The committee concluded that

the data from this subgroup is appropriate for decision making when only nivolumab is suitable (see section 3.4).

### Nivolumab improves progression-free survival and overall survival compared with chemotherapy alone

3.6 Data on progression-free survival and overall survival outcomes from the CheckMate 648 subgroup (see section 3.5) are academic in confidence and cannot be presented here. The committee concluded that nivolumab plus chemotherapy improves both progression-free survival and overall survival compared with chemotherapy alone.

## Indirect comparison with pembrolizumab

### There is uncertainty around the comparability of the trials included in the indirect treatment comparison

3.7 Nivolumab plus chemotherapy was indirectly compared with pembrolizumab plus chemotherapy in the absence of a direct trial comparison. Data for pembrolizumab came from the KEYNOTE-590 trial. There was no efficacy data from the KEYNOTE-590 population in whom nivolumab plus chemotherapy was suitable (tumour cell PD-L1 expression of 1% or more). The indirect treatment comparison (ITC) used outcomes from the population for whom pembrolizumab plus chemotherapy was suitable (PD-L1 expression with a CPS of 10 or more). Progression-free survival and overall survival outcome data from CheckMate 648 and KEYNOTE-590 were indirectly compared. In KEYNOTE-590, progression-free survival data was restricted to oesophageal cancer with squamous cell carcinoma or adenocarcinoma histologies, and overall survival data was restricted to squamous cell histology. A comparability assessment between the 2 trials showed that CheckMate 648 included more people with an Asian family background and fewer people had metastatic disease. The company compared some baseline characteristics from people in both trials whose tumours had PD-L1 expression with a CPS of 10 or more. The ERG agreed that this subgroup appeared comparable to the ITT populations in the trials. However, it was noted that conclusions around trial comparability are

limited because the only characteristics presented were age, Asian family background, Eastern Cooperative Oncology Group status and metastatic disease. Also, these characteristics were only available as an average of both trial arms in KEYNOTE-590 (pembrolizumab plus chemotherapy and chemotherapy alone).

One clinical expert highlighted that people in the 2 trials are likely to be comparable, based on the overall survival that was observed in the control arms of both trials. They also said there is little clinical understanding of how outcomes may differ by how PD-L1 expression was measured (tumour cell expression or CPS). Furthermore, they stated there is also uncertainty in how outcomes may differ in the broader oesophageal cancer population and in tumours which express PD-L1. Another clinical expert commented that while CheckMate 648 included only people with oesophageal squamous cell carcinoma, KEYNOTE-590 included people with squamous cell carcinoma and adenocarcinoma, located in either the oesophagus or the gastroesophageal junction. This made it difficult to reach any conclusions about trial comparability. The committee noted there was uncertainty about the comparability of the 2 trials used in the ITC.

## The indirect comparison does not give clear evidence of superiority of one treatment over the other

3.8 The company explored various ITC analyses to estimate the relative treatment effect of nivolumab plus chemotherapy versus pembrolizumab plus chemotherapy in terms of progression-free survival and overall survival. The company's analyses included people from CheckMate 648 for whom both nivolumab and pembrolizumab were suitable (see section 3.4). This generated time-varying progression-free survival hazard ratios (HRs) which favoured pembrolizumab plus chemotherapy from 3 months. The overall survival HRs favoured nivolumab plus chemotherapy after 6 months. The ERG's base-case analyses included people from CheckMate 648 for whom pembrolizumab was suitable (see section 3.4). These generated time-varying progression-free survival and overall survival HRs which favoured pembrolizumab plus chemotherapy over all time points. The ERG favoured including people for whom pembrolizumab was suitable, to maintain maximum trial comparability

because the information on suitability of nivolumab in KEYNOTE-590 was not available (see section 3.3 and section 3.7). The company and ERG base-case analyses also differed in the distributions used to extrapolate survival and which treatments were used as the baseline to scale pembrolizumab survival estimates. In both analyses, the HR credible intervals were wide and crossed 1. The ERG commented that the methodologies used in the ITC were robust and there were some arguments for using the company's base-case analysis. However, the ERG concluded that it was difficult to determine whether 1 treatment extended progression-free survival or overall survival more than the other.

The clinical experts maintained that the effectiveness of nivolumab and pembrolizumab (in terms of response or survival) is almost the same in other cancers, highlighting an immunotherapy 'class effect'. They expect this effect to be consistent in treating oesophageal squamous cell carcinoma tumours. They further explained that comparing nivolumab and pembrolizumab across different definitions of PD-L1 positivity and trial datasets was 'risky' in terms of validity. The CDF lead explained that pembrolizumab is administered less frequently than nivolumab, which may provide added benefit to people and also reduce the burden on NHS cancer services because fewer hospital visits would be needed.

The committee acknowledged the complexity of calculating a reliable relative treatment effect in the comparison of nivolumab and pembrolizumab. The clinical experts, company, ERG and committee all agreed that no definitive evidence of superiority of one treatment over the other had been presented.

# The company's economic model

## The company's economic model is appropriate for decision making

3.9 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of nivolumab plus chemotherapy compared with chemotherapy and pembrolizumab plus chemotherapy. The 3 health

states were progression-free survival, progressive disease, and death. The ERG agreed that the company's model structure captured all relevant health states and that partitioned survival models are widely used in cancer modelling. The ERG's concerns on the model structure related to the modelling of effectiveness associated with subsequent therapy. The company included a 2-year stopping rule for nivolumab. Although this is not included in the marketing authorisation, it reflects the use in the trial and expected use in clinical practice, in line with nivolumab use in other cancers. The committee concluded that the company's model structure was acceptable for decision making.

# Assumptions for the comparison with chemotherapy

## It is unclear which model for estimating overall survival is more appropriate

3.10 The company used Kaplan–Meier data from CheckMate 648 to model overall survival in both treatment arms, with a log-normal extrapolation from 6.9 months. The company justified the semi-parametric approach stating it better reflects the changing hazard observed after 20 months in both trial arms and noted a clear inflection point for the chemotherapy arm smoothed hazard plot at around 6 months. The ERG did not agree with the company's approach and used a parametric log-logistic extrapolation in their base case. It justified the parametric extrapolation by noting no clear inflection point for the nivolumab plus chemotherapy smoothed hazard plot. It also found a reasonable correspondence of the landmark overall survival observed in CheckMate 648 with the parametric overall survival analysis. The committee heard that a semi-parametric extrapolation of overall survival was broadly accepted by the committee in TA737. The committee acknowledged there was uncertainty in the long-term overall survival and there were arguments for each approach.

## In-trial switching may have had an impact on overall survival, but its effect is uncertain

3.11 There was evidence of treatment switching in CheckMate 648, with a proportion of both arms who had subsequent systemic and anti-PD-L1 therapies (including nivolumab and pembrolizumab). The company considered that a decreasing hazard rate (mortality rate) observed in the chemotherapy arm of CheckMate 648 was implausible. The ERG argued that it might be partly because of in-trial switching to an anti-PD-L1 therapy. The ERG also noted that, although only a fraction of people in the trial switched to an anti-PD-L1 therapy, the company assumed in its economic model that all people who had subsequent treatment in clinical practice would have an anti-PD-L1 therapy. The ERG suggested that this might lead to a bias where the effectiveness of chemotherapy had been underestimated in the economic model. To overcome the bias in results, it preferred an adjustment of overall survival in the model using methods outlined in NICE's Decision Support Unit technical support document 16. The company elected against including a switching adjustment in their base-case modelling of overall survival, commenting that few people switched to an anti-PD-L1 therapy in the trial. It also explained that the switching adjustment methods in the technical support document place large demands on limited data which can create more uncertainty. The company presented 2 switching adjustment scenario analyses: a rank-preserving structural failure time model and a model-based approach. As the incremental cost-effectiveness ratio (ICER) of nivolumab plus chemotherapy versus chemotherapy increased markedly in these scenarios, the ERG maintained that the ICER is underestimated without a switching adjustment. The committee heard that switching was not included in TA737. While the ERG acknowledged this, it again referred to the clinical evidence that it said demonstrated switching and the difference between the proportion switching in the trial and that which would occur in clinical practice. A clinical expert explained that switching to an anti-PD-L1 therapy may introduce some bias, but it was not expected to be impactful on overall survival. The committee concluded that the switching may have an impact on the overall survival in both trial arms, but that its overall impact was uncertain.

## It is reasonable to expect some treatment waning after treatment

## is stopped, but the impact on overall survival is uncertain

3.12 In its base case, the company assumed there was no waning of treatment effect after stopping nivolumab. It commented that there was evidence of a robust and durable treatment effect lasting beyond discontinuation for immunotherapies. It stated that if any treatment waning was to occur it would be 5 years after starting therapy. It referenced NICE's technology appraisal of nivolumab for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in which the committee considered a 5-year assumption of treatment waning to be plausible. The ERG disagreed with this assumption and included the waning of treatment effect on overall survival for nivolumab from 2.5 years to 4.0 years after starting therapy and 6 months after stopping therapy. The ERG justified the assumptions, explaining that for some overall survival parametric functions the nivolumab plus chemotherapy treatment effect versus chemotherapy alone increased over time, which was considered implausible. Additionally, the ERG highlighted that treatment waning assumptions were not disregarded by the committee in TA737. However, it noted that no conclusions about the appropriateness of waning were made by the committee. The company commented that there was no clear justification for the 2.5 years to 4.0 years treatment waning assumptions preferred by the ERG.

The clinical experts commented that some treatment waning is possible and it is more likely when nivolumab plus chemotherapy is discontinued early. The committee considered that based on the maturity of the data in CheckMate 648, the treatment effect may be captured within the observed results making an adjustment of the extrapolation of overall survival for treatment waning unnecessary.

The committee acknowledged that the treatment waning effect of pembrolizumab was discussed in TA737 and that no conclusions on the appropriateness of waning were stated in the final guidance. It concluded that assuming a lifelong treatment effect of nivolumab may be over optimistic and some treatment waning might be expected. However, there was not enough evidence to be precise about when this would occur. The committee concluded that it would consider scenarios with

and without treatment waning in its decision making, only if they impact the final decision on cost effectiveness.

## Modelling risk of death is uncertain, but has minimal impact on the cost-effectiveness estimates

3.13 The reduction in the risk of death in CheckMate 648 was similar to that of background mortality. The company and the ERG agreed that mortality should not be any lower than background (all-cause) mortality. To enforce a plausible minimum rate of mortality, a background mortality rate was included in the model, additional to the predicted overall survival. The company maintained that the approach resulted in very little difference in the overall survival. However, the ERG considered this approach to double-count mortality in the model and preferred the use of alternative methods which prevent implausibly low mortality hazard with any overall survival extrapolation. The committee acknowledged the justifications for each modelling approach but did not conclude which was preferable because each assumption had a minimal impact on the cost-effectiveness estimates.

## Treatment-specific health-related quality of life estimates are not considered appropriate

3.14 Utility values in the model were calculated using EQ-5D data from CheckMate 648. The company attributed utilities to the progression-based health states in its base case, using the average utility reported in the 2 trial arms. The ERG explained that because the EQ-5D scores reported were consistently higher for chemotherapy compared with nivolumab plus chemotherapy, treatment-specific utilities were more appropriate. The clinical experts suggested toxicity associated with nivolumab therapy may explain lower utility values compared with chemotherapy alone. The clinical experts stated that they would expect the opposite in practice, with people who had nivolumab plus chemotherapy likely to have higher utility because of better disease control. The CDF lead and clinical experts did not agree with using the treatment-specific utilities. This is based on their experience that health-related quality of life disutilities associated with anti-PD-(L)-1 immunotherapies toxicity would be outweighed by the health benefit

derived from response to therapy. Because treatment-specific utilities are clinically plausible, the committee concluded that treatment-specific utilities were not appropriate.

### There is uncertainty in the calculation of treatment costs weighted by delayed or missed doses

3.15 A proportion of people in CheckMate 648 delayed or missed doses of their trial treatment. In its base-case analysis, the company adjusted treatment costs based on the mean relative dose intensity observed in the trial. These treatment costs were then weighted by the time each patient spent on treatment. The ERG explained that time on therapy was not relevant for capturing the relative dose intensity and omitted this from its base case. The company stated that the treatment discontinuation biased the treatment cost calculations. The committee noted uncertainty in both approaches taken.

## End of life

### Nivolumab plus chemotherapy meets end of life criteria compared with chemotherapy, but not with pembrolizumab plus chemotherapy

3.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It considered whether nivolumab plus chemotherapy met the end of life criteria compared with chemotherapy for people in whom pembrolizumab is unsuitable. The company and ERG both agreed that data suggests that life expectancy in this population is less than 24 months. The observed median overall survival benefit with nivolumab plus chemotherapy in CheckMate 648 was larger than the additional 3-month extension to life needed by the criteria (data are academic in confidence and cannot be presented here). The committee considered whether nivolumab plus chemotherapy met the end of life criteria compared with pembrolizumab plus chemotherapy for people in whom pembrolizumab is suitable. The company and ERG both agreed, based on the KEYNOTE-590 analyses, that life expectancy in this

population is less than 24 months. Based on the ITC analyses (see section 3.8), the median overall survival benefit of nivolumab plus chemotherapy compared with pembrolizumab plus chemotherapy did not exceed the additional 3-month extension to life needed by the criteria (the data cannot be reported here because the company submitted it as academic in confidence). The committee concluded that nivolumab met the end of life criteria compared with chemotherapy but that criteria were not met compared with pembrolizumab plus chemotherapy.

# Cost-effectiveness estimate

## Nivolumab is unlikely to be cost effective when compared with pembrolizumab

3.17 The company's base-case comparison of nivolumab with pembrolizumab included the following assumptions:

- semi-parametric extrapolation of progression-free and overall survival data from CheckMate 648 for nivolumab (see section 3.10)
- excluding any adjustments to overall survival for subsequent therapy (see section 3.11)
- excluding nivolumab treatment waning (see section 3.12)
- including all-cause mortality, additional to the predicted overall survival mortality (see section 3.13)
- using progression-based utilities, independent of the treatment received (see section 3.14)
- adjusting treatment costs by the relative dose intensity, weighted by the time on treatment (see section 3.15).

  Differences in the company's and ERG's base case are in the methodology used for the ITC. The company base case used the following ITC analyses assumptions (see section 3.8):

- including outcome data from people in CheckMate 648 for whom both nivolumab and pembrolizumab was suitable and people from KEYNOTE-590 for whom pembrolizumab was suitable (see section 3.4)
- scaling nivolumab and pembrolizumab survival using chemotherapy as the baseline
- using log-normal distribution to extrapolate overall survival.

The ERG's base-case analyses differed from the company's because it included people from CheckMate 648 for whom only pembrolizumab was suitable. The company and ERG base-case analyses also differed in the distribution used to extrapolate survival and which treatment was used as the baseline to scale pembrolizumab survival estimates.

The ICERs cannot be reported here because of confidential commercial arrangements for nivolumab and pembrolizumab. The company's and ERG's base-case cost-effectiveness estimates were similar, both showing nivolumab plus chemotherapy to be dominated by pembrolizumab plus chemotherapy. The committee concluded that it was unlikely that nivolumab plus chemotherapy would be a cost-effective use of NHS resources when pembrolizumab is a suitable option.

## Nivolumab plus chemotherapy is cost effective when compared with chemotherapy alone when pembrolizumab is unsuitable

3.18 The company's comparison of nivolumab plus chemotherapy with chemotherapy for people in whom pembrolizumab is not suitable used the same assumptions as for the comparison with pembrolizumab plus chemotherapy (see section 3.17). The ERG's base case included the same assumptions as the company in its exclusion of an adjustment on survival for switching (see section 3.11). The ERG's assumptions differed from the company in the approach to modelling progression-free survival and overall survival, and parametric extrapolation was modelled with a waning of nivolumab treatment effect between 2.5 years and 4 years (see section 3.12). Additionally, treatment-specific progression utilities were included in the model (see section 3.14), and the relative dose intensity was not weighted by time on treatment (see section 3.15). The ICERs cannot be reported here because of confidential commercial

arrangements for nivolumab and subsequent treatments. Including the ERG's assumptions increased the ICER compared with the company's base case, however the company's cost-effectiveness estimates are below the end of life threshold of £50,000 per quality-adjusted life year (QALY) gained. While the ERG's cost-effectiveness estimates are above £50,000 per QALY gained, the committee did not agree with the assumption of treatment-specific utilities. Removing this assumption provided cost-effectiveness estimates which were below £50,000 per QALY gained. Because end of life criteria have been met (see section 3.16), the committee concluded that nivolumab plus chemotherapy is likely a cost-effective use of NHS resources when pembrolizumab is unsuitable.

# Equalities

## There are no equality issues relevant to the recommendations

3.19 Patient experts explained that people living in the most deprived areas are more likely to be diagnosed with oesophageal squamous cell carcinoma later than others. The committee noted that the issues surrounding the delays in diagnosis are unable to be addressed in technology appraisal guidance.

# Innovation

3.20 The company and patient experts stated that nivolumab plus chemotherapy has a number of benefits including improved efficacy outcomes compared with chemotherapy, maintenance of quality of life, an acceptable safety profile and providing an additional treatment option for people with high unmet need. They also stated that PD-L1 test results for suitability of nivolumab are available quicker than PD-L1 test results for suitability of pembrolizumab. This is because the CPS test is more complex than the tumour cell test and often needs to be requested from an external diagnostic centre. The committee concluded that it had not been presented with any evidence for benefits not captured in the model.

# Conclusion

## Nivolumab is recommended for routine use only when pembrolizumab is unsuitable

3.21 The committee noted that the company's and ERG's base-case conclusions aligned in that nivolumab plus chemotherapy was dominated by pembrolizumab plus chemotherapy, that is higher cost and lower efficacy. The committee acknowledged the uncertainty around relative treatment effects for the 2 treatments, but concluded that nivolumab plus chemotherapy was unlikely to be cost effective compared with pembrolizumab plus chemotherapy.

The committee noted that the company's base case suggested that nivolumab plus chemotherapy is likely to be cost effective compared with chemotherapy, for people for whom pembrolizumab is not suitable. This is when considering nivolumab as a life-extending treatment for people with short life expectancy (see section 3.17). The committee also noted that the ERG's base case suggested that it was unlikely to be cost effective compared with chemotherapy alone, even in the context of a life-extending treatment for people with a short life expectancy (see section 3.16). However, nivolumab was cost effective when treatment-specific utilities, which the committee deemed as inappropriate, were removed from the ERG's analyses and when considering end of life criteria (see section 3.17).

Despite the remaining areas of uncertainty, it was agreed that the cost-effectiveness estimates for nivolumab when pembrolizumab is not suitable are likely to be within the range usually considered a cost-effective use of NHS resources. This is for a life-extending treatment for people with short life expectancy. Therefore, nivolumab with platinum- and fluoropyrimidine-based chemotherapy is recommended for use in the NHS as an option for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma, in adults whose tumour cells express PD-L1 at 1% or more. It is recommended only if pembrolizumab plus chemotherapy is unsuitable. The committee recalled the current implementation issues for testing (see section 3.3). It

therefore also concluded that testing for suitability of nivolumab and pembrolizumab should be done at the same time.

# 4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this 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 previously untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma, in adults whose tumour cells express PD-L1 at a level of 1% or more and are unsuitable for pembrolizumab plus chemotherapy and the doctor

responsible for their care thinks that nivolumab in combination with platinum- and fluoropyrimidine-based chemotherapy is the right treatment, it should be available for use, in line with NICE's recommendations.

4.5 The committee heard there have been implementation issues for pembrolizumab (TA737) because of the required test to confirm suitability of the treatment. To minimise unnecessary delays to accessing treatment, assessments for treatment suitability of both pembrolizumab plus chemotherapy and nivolumab plus chemotherapy should be done concurrently.

# 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.

## Chair

**Radha Todd**
Chair, technology appraisal committee A

## 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.

**Owen Harrison**
Technical lead

**Louise Crathorne and Carl Prescott**
Technical advisers

**Jeremy Powell**

Project manager

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# Accreditation