NICE National Institute for Health and Care Excellence

NICE guidance

Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance 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.

Contents

1 Recommendations

1.1 Nivolumab is recommended, within its marketing authorisation, for adjuvant treatment of completely resected oesophageal or gastro-oesophageal junction cancer in adults who have residual disease after previous neoadjuvant chemoradiotherapy. It is recommended only if the company provides nivolumab according to the commercial arrangement.

Why the committee made these recommendations

The most common treatment for oesophageal or gastro-oesophageal junction cancer is neoadjuvant chemoradiotherapy then surgery. Treatment choice depends on various factors including histology, tumour size and location, patient preference and treatment suitability.

Clinical trial evidence shows that after trimodal therapy (chemoradiotherapy and surgery), nivolumab increases how long people live without the cancer returning compared with standard care, which is surveillance alone. Nivolumab is also likely to be more effective at extending how long people live, but clinical trial evidence is not yet available.

The cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources, so nivolumab is recommended.

2 Information about nivolumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol Myers Squibb) as monotherapy is indicated for 'the adjuvant treatment of adult patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy'.

Dosage in the marketing authorisation

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

Price

2.3 Nivolumab is available in 3 different sizes as a concentrate for solution for infusion vials. The cost varies according to vial size: £439 (40 mg per 4 ml), £1,097 (100 mg per 10 ml) and £2,633 (240 mg per 24 ml; excluding VAT; BNF online, accessed August 2021). The cost for 1 dose of treatment is £2,633 (240 mg per 24 ml).

2.4 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), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 3 issues were resolved during the technical engagement stage, and agreed that:

- The generalised F-distribution should be used to model disease-free survival in the nivolumab and routine surveillance arms.
- The average age of people included in the economic model should be 62.66 years. The company provided adjusted CheckMate-577 data that reflected the age distribution of people with oesophageal cancer who had chemoradiotherapy and surgical resection in the NHS.
- General population utility and post-recurrence utility should be adjusted for age using the Ara and Brazier adjustment factor. The company provided updated inputs for the economic model that amended an error causing utilities for the disease-free and recurred-disease health states to be equal after 75 years.

The committee recognised that there were 2 remaining areas of uncertainty associated with the 'cure' point and costs of treatment. It took these into account in its decision making.

The condition

There is high unmet need for adjuvant treatments in this area

3.1 Oesophageal cancer is a malignant tumour of cells lining the oesophagus. The 2 main types are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma usually affects the upper and middle oesophagus. Adenocarcinoma is more common in the UK and usually affects the lower oesophagus, including the gastro-oesophageal junction. Early symptoms may be vague, subtle and similar to benign conditions, which can result in late diagnosis and a poor prognosis. Clinical experts highlighted that the aim of treatment is to cure disease, but recurrence occurs for around 50% to 60% of people who have residual disease after chemoradiotherapy. The patient expert explained that people have ongoing fear because of a lack of available active treatments after surgery,

which affects mental wellbeing and quality of life. The committee concluded that there is an unmet need for active treatments for this condition, and that these would have physical and psychological benefits.

Treatment pathway

There is variation in current practice but the nivolumab marketing authorisation includes a specific population

3.2 Current standard care for oesophageal or gastro-oesophageal junction cancer depends on clinical evidence, histology and the patient's informed preferences. Clinical experts explained that most people who have squamous cell carcinoma have chemoradiotherapy then surgery. But a proportion of people have definitive chemoradiotherapy alone with no surgery, which is considered to be broadly equivalent. People who have adenocarcinoma may have either neoadjuvant chemoradiotherapy then surgery or perioperative FLOT (fluorouracil, folinic acid, oxaliplatin, docetaxel) chemotherapy. The clinical trial inclusion criteria included adults with oesophageal or gastro-oesophageal junction cancer who had neoadjuvant chemoradiotherapy and complete surgical resection with clear margins, but residual pathologic disease was present in the removed surgical specimen. The company indicated that the marketing authorisation corresponds with these criteria and people who have treatment with FLOT are not included. The clinical experts explained that this was a specific population who were identifiable in clinical practice in the NHS. They noted that over 80% of people have complete resection after chemoradiotherapy. Also, in the CROSS trial comparing neoadjuvant chemoradiotherapy plus surgery with surgery alone for oesophageal or gastro-oesophageal junction cancer, 92% of people who had chemoradiotherapy plus surgery had a complete resection. However, they explained that the presence of detectable residual disease in the surgical specimen depended on histology, with residual disease more likely in those with adenocarcinoma than squamous cancer. The committee can only appraise a technology within its licensed indication and the evidence supporting this appraisal was from a single clinical trial with a specific population, in line with the marketing authorisation. This means people who have had other treatments such as chemotherapy alone, or definitive chemoradiotherapy (with no surgery) are outside the scope of this appraisal. The committee concluded that people with completely resected oesophageal or gastro-oesophageal junction cancer who have residual

pathologic disease after neoadjuvant chemoradiotherapy would be the population considered in this appraisal, based on the clinical evidence available.

Evidence is only available for people who had surgical treatment in line with the CheckMate-577 trial protocol

3.3 The committee was aware that a proportion of people have definitive chemoradiotherapy with no pre-planned surgery, but could later have salvage resection. The clinical experts explained that there are 2 populations who might have delayed surgery in clinical practice. One population includes people in whom there is no intention to operate as part of the primary treatment, but resection is done if the cancer recurs. The committee noted that this population was different to the population included in the marketing authorisation and agreed it could not be considered for adjuvant nivolumab treatment. The second population are those in whom there is thought to be a high surgical risk. In those cases, definitive chemoradiotherapy may be used first to avoid surgery, followed by an early assessment after 2 or 3 months. Primary salvage resection is then done if residual disease is found. The clinical lead for the Cancer Drugs Fund explained that primary salvage resection may have been allowed in the clinical trial if the window of time between chemoradiotherapy and resection covered the 2- to 3-month assessment point. The committee agreed that only people who had salvage resection within the window included in the trial protocol could be considered equivalent and would be eligible for treatment with adjuvant nivolumab.

Clinical evidence

CheckMate-577 is generalisable to current clinical practice in the NHS

3.4 Clinical evidence was based on CheckMate-577, a phase 3, multicentre, randomised, double-blind, placebo-controlled trial that included a very small number of people from the UK. It compared nivolumab monotherapy with placebo. The committee noted that baseline characteristics were well balanced between arms. But the ERG advised that there were several differences between the population in CheckMate-577 and the population in the NHS:

- The average age in the full population was 62, which is younger than in the NHS.

- The proportion of men was higher in the trial than in the NHS.
- The proportion of different ethnicities in the trial was likely to be different to those seen in the NHS.

The patient expert explained that younger people and more women are now being seen in clinical practice. The clinical experts agreed but noted that these demographic changes were unlikely to be reflected in current clinical trials and that differences in age, sex and ethnicity were unlikely to affect the clinical efficacy of nivolumab. On balance they considered the trial to be generalisable to the NHS and also agreed that the distribution of histology in the trial reflected the population seen in the NHS. The committee concluded that data from the CheckMate-577 trial was generalisable to the NHS and could be used for the clinical-effectiveness analyses.

Nivolumab is clinically effective and extends disease-free survival compared with placebo

3.5 The primary outcome in the CheckMate-577 trial is disease-free survival. The February 2021 data cut showed that nivolumab increased disease-free survival compared with placebo (hazard ratio 0.67, 96% confidence interval 0.55 to 0.81). The median disease-free survival in people who had nivolumab was 22.4 months and 10.4 months with placebo. Results for overall survival are not yet available. The clinical lead for the Cancer Drugs Fund and clinical experts agreed that the disease-free survival Kaplan–Meier data showed a clear separation between the curves. This shows that more people were disease-free who had nivolumab than those who had placebo. The clinical expert also noted that this data showed that some people are likely to never have disease recurrence, and that this proportion is higher for those who had nivolumab. The committee concluded that, based on the CheckMate-577 results, adjuvant nivolumab is clinically effective and extends disease-free survival compared with placebo.

Disease-free survival is a reasonable outcome to consider for modelling because of the extended follow up

3.6 The committee was aware that the company used disease-free survival results in the economic model because no overall survival data was available. The company explained that overall survival was a secondary end point in the clinical trial, which was event driven. The data remained immature and so the company

did not yet have access to the overall survival data and remained blinded to the results. The company assumed a benefit for overall survival (assuming that if the disease recurred there would be equal mortality for those who had placebo or nivolumab). Both the clinical experts and clinical lead for the Cancer Drugs Fund had agreed that the disease-free survival benefit shown for nivolumab was compelling. Assuming an overall survival benefit based on a surrogate end point, in this case disease-free survival, is uncertain. The committee was aware this has been subject to much debate in previous appraisals, in some of which surrogate outcomes had proven unreliable. However, the ERG noted that the evidence in these cases came from highly heterogeneous populations and had short follow ups. So, it did not reflect the data available for CheckMate-577, where at least 44 months of follow up was available for disease-free survival, which is close to the time point the ERG considered reasonable to assume a 'cure'. The committee agreed that given the extended follow up this was a suitable outcome to use for modelling survival and that the assumption of overall survival benefit was reasonable.

Nivolumab may be more effective for people who have squamous cell carcinoma, but it is beneficial regardless of histology

3.7 The committee considered the subgroup results from CheckMate-577. The latest results are considered confidential and cannot be reported here. The committee was aware that the trial was not powered to test for statistical significance of an interaction between treatment and subgroups. But the results showed that nivolumab appeared more effective in squamous cell carcinoma than adenocarcinoma. The clinical experts advised that survival curves from the CROSS trial suggested that people who have squamous cell carcinoma have better outcomes than those who have adenocarcinoma, based on current standard care, and that squamous cell carcinoma may respond better to treatment. However, both histological types appeared to benefit from adjuvant nivolumab. The company and ERG highlighted that, despite not being powered for subgroups, the results showed hazard ratios less than 1 for almost all pre-specified subgroups. The committee concluded that nivolumab may be more effective for people who have squamous cell carcinoma, but it is beneficial regardless of histology.

Nivolumab is generally well tolerated and adverse events are included in the economic modelling

3.8 In CheckMate-577 a similar number of people experienced adverse events in the nivolumab and placebo arms. The clinical experts highlighted in their written submissions that serious adverse events can happen after treatment with nivolumab that need additional management and monitoring. The clinical lead for the Cancer Drugs Fund explained that as there are now improved clinical systems to detect and treat immune-mediated toxicities of nivolumab, serious side effects are rarer than previously seen. The ERG and the company confirmed that all serious adverse events were considered in the economic modelling. The committee concluded that adverse events are adequately included in the economic modelling.

Cost effectiveness

The company's model is appropriate for decision making

3.9 The company presented a 3-state semi-Markov model to estimate the cost effectiveness of nivolumab compared with standard care. The 3 health states were disease-free, recurrent disease and death. The company explained that a partitioned survival model was not possible because of unavailable overall survival data, but the semi-Markov model allows dependency between events rather than using priori assumptions in traditional Markov models. The ERG agreed with this approach. The model cycle length was 1 week, and the time horizon was 40 years. No half-cycle correction was included in the model. The ERG noted that this was not a limitation because of the weekly time cycles used in the model. The committee had already concluded that disease-free survival was a suitable outcome given the extended follow up in CheckMate-577. It recalled that the company assumed an overall survival benefit and equal deaths after recurrence. The ERG explained that the company used external data from Lou et al. to apply a mortality rate to both arms. The company had explored alternative assumptions and sensitivity analyses on this parameter that showed broadly similar results when applied to both arms. The committee concluded that the company's semi-Markov model was suitable for decision making.

Survival extrapolations

The generalised F-distribution gives the most appropriate long-term estimate of disease-free survival

3.10 In its original submission the company modelled disease-free survival using a 1-knot spline log-normal distribution. The ERG noted that the generalised F-distribution had a better statistical fit to the trial data. More recent disease-free survival data became available from the CheckMate-577 trial after the original submission data. Therefore, after technical engagement, the company updated its analysis to use the recent cut-off data (February 2021). In addition, the company updated the distribution used to model disease-free survival to a generalised F-distribution because it provided the lowest AIC (Akaike's Information Criteria) and BIC (Bayesian Information Criteria) values. The company noted that the 1-knot spline distribution remained plausible and provided results in scenario analyses. The committee agreed that the generalised F-distribution was suitable and gave the most appropriate estimate of long-term disease-free survival.

People who are free from cancer at 5 years are unlikely to have recurrence and can be considered 'cured'

3.11 In its base case, the company assumed that all patients who were alive and disease free at 3 years were 'cured' of cancer, that is, it would not recur. After 3 years, people in the disease-free health state were modelled with the same mortality risk as the general population. The 3-year cure assumption was based on results from CheckMate-577, which showed a low risk of recurrence after 2 years, and clinical advice given to the company. The clinical experts explained that the Kaplan–Meier curves from CheckMate-577 showed a plateau at around 36 months, suggesting that few relapses happened after 3 years. So, this was a reasonable cure point assumption. The ERG preferred a 'cure' point at 5 years disease-free survival, noting that some disease recurrence happened after 3 years and that a longer duration before assuming cure was more plausible. The company highlighted the low frequency of events after 3 years. However, the committee considered that although a precise 'cure' point was uncertain, it had concerns about applying a 3-year cure point and preferred the ERG's 5-year assumption. It concluded that a cure point at 5 years was plausible.

The mortality rate of people who are 'cured' of cancer is likely to be higher than that of the general population

3.12 In both the company and ERG base case the cure point assumes that all patients who are alive and disease free at that time have 'cured' cancer and have the same mortality rate as the general population. This indicated not just no recurrence, but also that the quality of life and life expectancy would then be the same as a person who had not had the disease. The committee recalled that nivolumab treatment would involve chemoradiotherapy, major surgery and immunotherapy. In addition, there were risk factors that can pre-dispose people to oesophageal cancer, which may increase background mortality rates. The patient expert explained that there are health consequences associated with a trimodal treatment pathway (chemoradiotherapy and surgery) followed by nivolumab. For example, fatigue and nutritional issues are potential lasting effects from surgery and chemoradiotherapy. The patient expert highlighted that people define themselves as disease-free survivors rather than 'cured' because of these lasting effects. The company explained it had clinical advice that people can be considered disease free after resection, but the risk of death may not become the same as the general population for 3 to 5 years. The committee therefore considered a scenario analysis where the mortality rate of people who are 'cured' of cancer is higher than that of the general population. This was done by modelling survival using an uplifted general population mortality rate (standardised mortality ratio of 1.1). This meant the probability of death was increased by an arbitrary 10% for all patients aged 68 and over. The clinical experts explained that an increase in mortality was likely to be because of treatment effects experienced by patients. For instance, there may be an increased risk of heart disease and lung damage for people who have had chemoradiotherapy. The clinical experts agreed that there are background environmental and genetic factors and a 10% increase in mortality was reasonable and unlikely to be higher. However, implementing this increased mortality risk had a minimal effect on the incremental cost-effectiveness ratio (ICER). The committee agreed that the mortality rate of people who are 'cured' of cancer is likely to be higher than that of the general population. It concluded that that a standardised mortality ratio of 1.1 was arbitrary and may not capture all the long-term effects, but this did not have a significant effect on the cost-effectiveness results.

Costs in the economic model

It is appropriate to apply a dose modifier to reflect the 1-year stopping rule for nivolumab

3.13 In the economic model, the company originally assumed that clinicians would stop treatment with nivolumab after 1 year. This was in line with the CheckMate-577 protocol and the summary of product characteristics. However, the ERG noted that the average time people had treatment in the clinical trial was 63 weeks so costs could have been underestimated in the model. Clinical experts confirmed that in clinical practice, they would stop treatment with nivolumab after 1 year or a maximum number of cycles in people whose disease had not recurred. The company and clinical experts explained that the additional time on treatment in the clinical trial was a result of dose delays and not people having additional treatment cycles. The clinical experts explained that allowing treatment up to 63 weeks in the model could overestimate costs. To align the benefit and time on treatment the company provided updated data from CheckMate-577 after technical engagement and applied a dose modifier to the time on treatment in the model. This meant that the number of cycles were effectively capped to 1 year. The clinical lead for the Cancer Drugs Fund confirmed that a stopping rule would be implemented so that people would have 52 weeks' worth of treatment. An equivalent of 13, 4-weekly treatment cycles could be implemented, and they explained that there is a lot of experience implementing this in clinical practice. The committee concluded that it was appropriate to apply a dose modifier to reflect the 1-year stopping rule for nivolumab and align costs and benefits in the economic model.

Cost-effectiveness estimates

Nivolumab is cost effective compared with routine surveillance

3.14 The committee agreed that its preferred assumptions to compare nivolumab with routine surveillance included:

- The generalised F-distribution to model disease-free survival in the nivolumab and routine surveillance arms.
- An average age of 62.66 years for people included in the economic model.

- General population utility and post-recurrence utility adjusted for age using the Ara and Brazier adjustment factor.
- A dose modifier to represent the 1-year stopping rule.
- People in the disease-free state have no further risk of disease recurrence after 5 years.
- A standardised mortality ratio of 1.1 to reflect the mortality rate of people who are 'cured' of cancer as higher than that of the general population after 5 years.

The committee considered the ICER for both the ERG and company's base cases for nivolumab compared with routine surveillance, which differed only in the application of the 'cure' point. The committee noted that all estimates of cost effectiveness were less than £20,000 per quality-adjusted life year gained. It concluded that nivolumab is a cost-effective use of resources in the NHS compared with routine surveillance.

Other factors

Nivolumab is a step change for people with oesophageal or gastro-oesophageal junction cancer, but the model captures all benefits

3.15 The company, clinical experts and patient experts stated that adjuvant nivolumab represents a step change in treatment for people with oesophageal or gastro-oesophageal junction cancer and that there is high unmet need for this population. The committee recalled that there are currently no active treatments available for this population. The company and clinical experts explained that treatment with nivolumab was well tolerated, would be beneficial to wellbeing, and would improve clinical outcomes. The committee noted that the treatment could be curative in some people, which would transform their quality of life. It concluded that nivolumab is a step change for people with oesophageal or gastro-oesophageal junction cancer, but all the benefits are captured in the cost-effectiveness estimates.

Conclusion

Nivolumab is recommended for routine commissioning

3.16 The committee agreed that the most plausible ICERs for nivolumab compared with current standard care were within what NICE normally considers to be an acceptable use of NHS resources. It therefore concluded that it could recommend nivolumab for the adjuvant treatment of completely resected oesophageal or gastro-oesophageal junction cancer in adults who have residual disease after neoadjuvant chemoradiotherapy.

4 Implementation

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

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

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has completely resected oesophageal or gastro-oesophageal junction cancer and had residual disease after previous neoadjuvant chemoradiotherapy and the doctor responsible for their care thinks that nivolumab 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.

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Accreditation