NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma cancer [ID2712]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma cancer [ID2712]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	BMS	**Has all the relevant evidence been taken into account?** All relevant evidence has been taken into consideration. No additional data will be presented.	Thank you for your comment.
2	Company	BMS	**Are the summaries of clinical and resource savings reasonable interpretations of the evidence?** The summaries of clinical evidence are reasonable interpretations of the evidence. However, BMS does not agree that pembrolizumab is the most relevant comparator for patients with PD-L1 combined positive score (CPS) ≥ 10. Further, the addition of CPS testing on top of the TC testing required for nivolumab may delay patients' access to timely effective treatment, as confirmed by clinicians.	Thank you for your comment. Responses to the issues the company raised are listed at comment number 4 – 6.
3	Company	BMS	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The current recommendation allows access to immunotherapy for patients with advanced oesophageal squamous cell carcinoma (OSCC) who do not qualify for pembrolizumab with chemotherapy. However, the current wording cannot be considered sound and a suitable basis for guidance to the NHS, the reasons for which have been described below and confirmed by oncology and pathology experts in upper GI cancers consulted as part of this response.	Thank you for your comment. Responses to the issues the company raised are listed at comment number 4 – 6.
4	Company	BMS	*Chemotherapy is the most relevant comparator for this indication* For all patients with 1L OSCC, chemotherapy is the comparator of choice. Although pembrolizumab with chemotherapy is available for patients with PD-L1 CPS ≥ 10, few patients receive this treatment. The Appraisal Consultation Document (ACD) quotes clinical experts who agree that pembrolizumab plus chemotherapy is widely used when it is suitable.[1] However, it was discussed at the ACM that the uptake of pembrolizumab with chemotherapy is slow and has reached a plateau, in line with the NICE budgetary assumptions for the pembrolizumab HTA.[2,3] During the ACM, a NHSE clinical expert confirmed that around 100 patients are receiving pembrolizumab for treatment of OSCC and that this figure is in a steady state. Corroborating this, clinical experts noted in subsequent engagements that uptake of pembrolizumab plus chemotherapy in clinical practice has been less than expected. It is estimated that a total of 1,956 OSCC patients are eligible for first-line each year (see the Company Budget Impact Analysis Submission for further calculations). While it should be recognised that a proportion of patients will not be suitable for first-line treatment	The committee recognised that in clinical practice there were implementation issues for pembrolizumab. However, the clinical experts and the CDF lead agreed that pembrolizumab should be considered as a comparator for this appraisal. The committee's duty 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 cannot exclude a NICE-

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			(contraindication, low performance score/fitness, etc.), the CheckMate-648 and Keynote-590 trials indicate that approximately half of these 1,956 patients (~978) achieve a CPS score of ≥10 and, thus, are eligible for treatment with pembrolizumab plus chemotherapy.4,5 The NHSE clinical expert's figure of 100 patients with OSCC treated with pembrolizumab plus chemotherapy falls short of the estimate of eligible patients and indicates that chemotherapy would be the most relevant comparator for this appraisal.	recommended cost-effective comparator treatment which is available and used, such as pembrolizumab. The committee therefore concluded that pembrolizumab was also a relevant comparator, but it concluded that the testing for both drugs should be done concurrently to minimise unnecessary delays in accessing treatments. See FAD section 3.3
5	Company	BMS	This shortfall in expected uptake of pembrolizumab with chemotherapy compared to the actual eligible population suggests that there is a significant number of otherwise eligible patients who do not receive immunotherapy. The reason(s) for this are open to question and are discussed below. Challenges with biomarker testing in clinical practice are preventing access to effective treatment options, impacting patients and adding burden to the NHS The current recommendation that nivolumab is "recommended only if pembrolizumab plus chemotherapy is not suitable" obligates clinicians to perform two biomarker tests to access treatment, as stated in the Blueteq form for interim funding of this indication.[6] Clinical experts consulted as part of this response have stated that this wording will be problematic when applied in real-world clinical practice. The reasons for this have been outlined below. *Impact on patients and burden on NHS: Delay to initiation of combined IO-chemo treatment* The wording, "recommended only if pembrolizumab plus chemotherapy is not suitable", implies sequential testing. This may cause delays in access to treatment as patients will have to have a CPS and TC score to be able to receive nivolumab, increasing the burden on pathologists and clinicians. The end-to-end process of CPS testing (order of the test to receipt of the result) is more complicated than TC testing. TC testing is more readily available and can be performed locally with faster turnaround times. If only this test is required for treatment with nivolumab then it will mean patients will be able to access treatment with nivolumab in a timely manner. Clinical experts have voiced concerns regarding the turnaround time of CPS testing and would anticipate that most patients will experience a delay of around three weeks until results are received. This is especially important in this population with advanced disease since any delay in initiating treatment may impact their long-term outcomes. *Impact on patients and burden on NHS: Complexities in testing can introduce unnecessary burden on pathology departments* Dual testing (be it sequential or in parallel) as opposed to PD-L1 TC testing only, per the MHRA license for nivolumab Dual testing (be it sequential or in parallel) as opposed to PD-L1 TC testing only,	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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			per the MHRA licence for nivolumab in this indication,[7] introduces unnecessary complexity. In practice, establishing eligibility for nivolumab plus chemotherapy under the proposed reimbursement criteria would require that both assays are performed on the tumour tissue specimen. As CPS testing has a different scoring methodology which requires more specialist expertise than PD-L1 TC, this cannot be as easily performed in-house. As both tests will likely need to be undertaken in order to prescribe nivolumab plus chemotherapy treatment, this will increase the burden on pathology departments, essentially doubling the assay requirements for each patient. The PD-L1 IHC assays are companion diagnostics and therefore the assay that was used in the trial should be used to determine eligibility for their respective therapy. The current recommendation for nivolumab and its implication of sequential testing is likely to further strain an already pressured testing environment. The potential, highly unfavourable, outcome is the delay in patients starting combined immunotherapy-chemotherapy treatment.	
6	Company	BMS	*Conclusion* The proposed recommendation for nivolumab plus chemotherapy for patients with first-line OSCC should not be limited to those unsuitable for pembrolizumab. As stated above, pembrolizumab is not yet standard of care in 1L OSCC patients with CPS ≥10 with most patients still receiving chemotherapy. Nivolumab has demonstrated that it is a cost-effective use of NHS resources in these patients when compared to chemotherapy and therefore should be made available for all first-line OSCC patients with PD-L1 TC ≥1. Furthermore, the additional burden caused by sequential testing of CPS and TC score to identify patients suitable for nivolumab under the current recommendation may delay patients' access to effective treatment options and add significant burden to the NHS, particularly over-stretched pathology departments. Therefore, the recommendation should allow prescribers to decide which treatment option will be most suitable for their patients and not delay access to treatment. Accordingly, alternative wording options may include: • "It is recommended where pembrolizumab plus chemotherapy is not suitable, or where access to CPS testing will delay combined treatment with immunotherapy" • "It is recommended where pembrolizumab is not suitable or if a CPS test result is not readily available" *References* 1. National Institute for Health and Care Excellence. Appraisal consultation document - Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma [ID2712]. 2022 [accessed 07/10/2022].	The committee recognised that in clinical practice there were implementation issues for pembrolizumab. However, the clinical experts and the CDF lead agreed that pembrolizumab should be considered as a comparator for this appraisal. The committee's duty 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 cannot exclude a NICE-recommended cost-effective comparator treatment which is available and used, such as pembrolizumab. The committee therefore concluded that pembrolizumab was also a relevant comparator, but it concluded that the testing for both drugs should be done concurrently to minimise unnecessary delays in accessing treatments. See FAD section 3.3.

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			2. National Institute for Health and Care Excellence. Technology appraisal guidance TA737. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer. 2021. Available from: https://www.nice.org.uk/guidance/ta737 [accessed 05/01/2022]. 3. National Institute for Health and Care Excellence. Resource impact template: Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). 2021. Available at: https://www.nice.org.uk/guidance/ta737/resources/resource-impact-template-excel-9263083501 [Accessed 01/11/2022]. 4. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022;386(5):449-62. 5. Sun J-M, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. The Lancet. 2021;398(10302):759-71. 6. NHS England. National Cancer Drugs Fund List ver1.236 (page 25). 2022. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.236.pdf [Accessed 01/11/2022]. 7. Medicines and Healthcare products Regulatory Agency. Summary of Product Characteristics - OPDIVO 10 mg/mL concentrate for solution for infusion. 2022. Available at: https://mhraproducts4853.blob.core.windows.net/docs/bbf7c1c30db8bc259f2f370e757ec51892be05bd [Accessed 01/11/2022].	
7	Company	BMS	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The committee recognised that patients and clinicians would welcome a new effective treatment for untreated adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma as currently these patients have a poor prognosis which has a significant impact on their quality of life.	Thank you for your comment.
8	Consultee	NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows. This assessment means that patients with squamous oesophageal cancer could have delayed access to effective treatment with nivolumab because of waiting for test results for PD-L1. There is already a minimum two-week delay for centres (the majority) who do not test in-house for PD-L1. As this assessment means that CPS will be tested before TPS and this is unlikely to be done at the same time due to the cost of the test, if CPS is not positive, then there will be another wait of two weeks for TPS results. Patients with oesophageal squamous cancer are unwell and symptomatic of their disease with	Thank you for your comment. The committee noted the implementation issues for pembrolizumab and at the second appraisal committee meeting strongly concluded that tests for pembrolizumab and nivolumab suitability should be done concurrently. This is to minimise

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			poor nutrition due to a blocked oesophagus. Even though chemotherapy can be started before PD-L1 results are known, this OSCC responds poorly to chemotherapy alone. Waiting four weeks for a treatment (nivolumab) which can improve response rates, nutrition and survival is unnecessarily long and some patients may fail to benefit from their chemotherapy alone and possibly stop treatment whilst waiting for these results.	unnecessary delays in accessing treatment.
9	Consultee	NCI-ACP-RCP-RCR	Secondly, for patients with OSCC, there is often very little tumour in the diagnostic biopsy, and it is likely that a significant number of patients will have insufficient tissue available for a second PD-L1 test. In this case some oncologists may chose not to treat with immunotherapy, or, in the alternative a patient may have a second invasive biopsy (with risks) followed by a further wait for test results.	Thank you for your comment. The committee noted the implementation issues for pembrolizumab and at the second appraisal committee meeting strongly concluded that tests for pembrolizumab and nivolumab suitability should be done concurrently. This is to minimise unnecessary delays in accessing treatment.
10	Consultee	NCI-ACP-RCP-RCR	As discussed in the appraisal, in my view it is fundamentally incorrect to compare nivolumab-chemotherapy with pembrolizumab-chemotherapy as the intention of the CheckMate 648 trial was to compare the combination with chemotherapy. Chemotherapy and pembrolizumab has not yet been firmly established as a standard of care, because access to and visibility of PD-L1 testing has been challenging. The committee goes on to note that “there was uncertainty about the comparability of the 2 trials used in the ITC.” which supports this argument.	The committee recognised that in clinical practice there were implementation issues for pembrolizumab. However, the clinical experts and the CDF lead agreed that pembrolizumab should be considered as a comparator for this appraisal. The committee’s duty 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 cannot exclude a NICE-recommended cost-effective comparator treatment which is available and used, such as pembrolizumab. The committee therefore concluded that pembrolizumab was also a relevant comparator, but it concluded that the testing for both drugs should be done concurrently to minimise unnecessary

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				delays in accessing treatments. See FAD section 3.3
11	Commentator	UKIOG	To whom in concerns re NICE TA 10572, We are writing on behalf of the UK and Ireland Oesophagogastric Cancer Group (UKIOG) which is a newly established umbrella group representing oncologists, surgeons, gastroenterologists, and all other medical and non-medical staff involved in the care of patients with oesophageal cancer. We are concerned that the new NICE guidance on nivolumab for advanced oesophageal squamous cancer may disadvantage patients for several reasons. The proposed guidance suggests that patients are tested for PD-L1 using both CPS and TPS scoring systems and that only patients who have PD-L1 CPS score of 1% will be eligible for nivolumab. Currently, only seven centres in the country offer PD-L1 CPS testing and as a result, most patients have PD-L1 requested externally. This can take two weeks or more to result. As patients with oesophageal squamous cancer often present with advanced disease and nutritional deficiency due to dysphagia being able to start the most effective treatment early is critical. Tumour response to treatment enables better nutrition and avoids the need for invasive treatments such as stents or tubes for feeding. In CheckMate 648 chemotherapy alone was associated with response rates of 20%, and this was more than doubled to 53% by the addition of nivolumab. As chemotherapy with nivolumab cannot be started until PD-L1 CPS and TPS status is known, introducing a significant delay in improved response rates will have a knock-on effect on patient wellbeing, and there is no doubt that some patients who need a quick response will be disadvantaged by this approach. In contrast, PD-L1 TPS scoring is much less specialised than PD-L1 CPS scoring and could likely be done “in-house” for most trusts, giving patients a result in a day or two and not delaying the institution of the most effective treatment. Secondly, the requirement for PD-L1 testing for both CPS and TPS introduces a significant risk that patients may not have sufficient tissue for both tests. Oesophageal squamous cancer is a tumour which often has scanty cells present on diagnostic biopsy. After testing one PD-L1 assay, there may be insufficient tissue available for a second. If this occurs, the patient will be ineligible for immunotherapy unless a second, invasive biopsy is performed. Endoscopy and biopsy is an invasive procedure which carries a small but non-negligible risk of aspiration, perforation and death. Furthermore, endoscopy waiting lists are a week or two even for cancer referrals, thus introducing even more potential delays into the patient receiving effective therapy. Finally, we disagree with the model used to compare chemotherapy and nivolumab with standard of care in the NICE assessment. In the CheckMate 648 trial, nivolumab plus chemotherapy showed a survival benefit compared to chemotherapy alone. In the NICE assessment, nivolumab plus chemotherapy was compared not to chemotherapy alone but with chemotherapy plus pembrolizumab which is not the correct comparator. Chemotherapy plus pembrolizumab is not universally adopted thus far as a standard of care, partly due to the challenges associated with PD-L1 CPS testing as discussed above. The CheckMate 648 trial which established nivolumab completed very slightly after the study which established pembrolizumab in this setting (KEYNOTE 590), but it seems that the earlier trial (KEYNOTE 590) has now moved the bar for marginally later studies which were United Kingdom & Ireland Oesophagogastric Cancer Group conducted in good faith. If this is the case, then it	The committee recognised that in clinical practice there were implementation issues for pembrolizumab. However, the clinical experts and the CDF lead agreed that pembrolizumab should be considered as a comparator for this appraisal. The committee’s duty 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 cannot exclude a NICE-recommended cost-effective comparator treatment which is available and used, such as pembrolizumab. The committee therefore concluded that pembrolizumab was also a relevant comparator, but it concluded that the testing for both drugs should be done concurrently to minimise unnecessary delays in accessing treatments. See FAD section 3.3

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			seems that later trials will never add value or be assessed fairly by NICE, which could lead to fewer trials and new treatments being delivered for patient benefit. In summary, we as an organisation would respectfully reconsider the current recommendation for PD-L1 testing in advanced oesophageal squamous cancer with respect to nivolumab. For patients to achieve safe and timely access to immune checkpoint inhibitors, we recommend that nivolumab is made achievable using the criteria established in the landmark CheckMate 648 trial.	
12	Commentator		As a GI molecular pathologist currently involved in setting up PDL1 testing pathways, the current proposal will significantly add to the complexity and workload when we are already struggling to provide a core diagnostic service. RCPath have shown that only 3% of pathology departments are adequately staffed at the present time. It would be more deliverable to have a single test based on tumour type e.g. TPS >1% for Nivo rather than requiring a two stage approach of CPS then TPS. We use the 22C3 clone for Pembro decisions scored by CPS and would then need to restain with 28.8 clone for Nivo and score by TPS. This doubles the cost of the testing and the resources required. Testing will almost certainly happen sequentially as we do not have capacity to test both upfront unless these tests are to be centrally commissioned with new money and resources flowing through (though we still need to generate additional staffing even if funded). TPS for Nivo would therefore be delayed if it follows CPS for Pembro. TPS is less labour intensive to score than CPS. From a lab perspective, keeping the pathway simple and avoiding duplication of testing will ensure that test results are available at the right time. Performing two separate tests (different antibodies and different scoring systems) risks this pathway failing in my opinion.	The committee recognised that in clinical practice there were implementation issues for pembrolizumab. However, the clinical experts and the CDF lead agreed that pembrolizumab should be considered as a comparator for this appraisal. The committee's duty 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 cannot exclude a NICE-recommended cost-effective comparator treatment which is available and used, such as pembrolizumab. The committee therefore concluded that pembrolizumab was also a relevant comparator, but it concluded that the testing for both drugs should be done concurrently to minimise unnecessary delays in accessing treatments. See FAD section 3.3
13	Commentator		Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes	Thank you for your comment.
14	Commentator		**Has all of the relevant evidence been taken into account? Yes, it has been** It would be recommended to take in CHECKMATE data in adenocarcinoma where Nivolumab was used as a 3 weekly regimen to assess the safety and efficacy of 3 weekly schedule. This is necessary	Thank you for your comment.

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			as most centres in UK offering chemotherapy to patients with advanced oesophageal SCC will do so as a 3 weekly Oxaliplatin + Fluoromyridine combination and hence restricting the guidance to 2/4weekly Nivolumab will create significant issues with treatment delivery.	
15	Commentator		**Are the recommendations sound and a suitable basis for guidance to the NHS?** I do not think that it is helpful to say that the combination of Nivolumab and chemo can be used for patients where Pembrolizumab combination is not suitable. Clinicians should have the freedom to choose which regimen they seem best fit for their patients if NICE committee feels that both treatments are effective in this disease area.	The committee recognised that in clinical practice there were implementation issues for pembrolizumab. However, the clinical experts and the CDF lead agreed that pembrolizumab should be considered as a comparator for this appraisal. The committee's duty 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 cannot exclude a NICE-recommended cost-effective comparator treatment which is available and used, such as pembrolizumab. The committee therefore concluded that pembrolizumab was also a relevant comparator, but it concluded that the testing for both drugs should be done concurrently to minimise unnecessary delays in accessing treatments. See FAD section 3.3
16	Commentator		**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No	Thank you for your comment.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

Response to the

Appraisal Consultation Document

Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1%

ID2712

Bristol-Myers Squibb Pharmaceuticals Ltd.

November 2022

Contents

1. Has all the relevant evidence been taken into account?

All relevant evidence has been taken into consideration. No additional data will be presented.

2. Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

The summaries of clinical evidence are reasonable interpretations of the evidence.

However, BMS does not agree that pembrolizumab is the most relevant comparator for patients with PD-L1 combined positive score (CPS) ≥ 10. Further, the addition of CPS testing on top of the TC testing required for nivolumab may delay patients' access to timely effective treatment, as confirmed by clinicians.

3. Are the recommendations sound and a suitable basis for guidance to the NHS?

The current recommendation allows access to immunotherapy for patients with advanced oesophageal squamous cell carcinoma (OSCC) who do not qualify for pembrolizumab with chemotherapy. However, the current wording cannot be considered sound and a suitable basis for guidance to the NHS, the reasons for which have been described below and confirmed by oncology and pathology experts in upper GI cancers consulted as part of this response.

Chemotherapy is the most relevant comparator for this indication

For all patients with 1L OSCC, chemotherapy is the comparator of choice. Although pembrolizumab with chemotherapy is available for patients with PD-L1 CPS ≥ 10, few patients receive this treatment. The Appraisal Consultation Document (ACD) quotes clinical experts who agree that pembrolizumab plus chemotherapy is widely used when it is suitable.[1] However, it was discussed at the ACM that the uptake of pembrolizumab with chemotherapy is slow and has reached a plateau, in line with the NICE budgetary assumptions for the pembrolizumab HTA.[2,3]

During the ACM, a NHSE clinical expert confirmed that around 100 patients are receiving pembrolizumab for treatment of OSCC and that this figure is in a steady state. Corroborating this, clinical experts noted in subsequent engagements that uptake of pembrolizumab plus chemotherapy in clinical practice has been less than expected. It is estimated that a total of 1,956 OSCC patients are eligible for first-line each year (see the Company Budget Impact Analysis Submission for further calculations).

While it should be recognised that a proportion of patients will not be suitable for first-line treatment (contraindication, low performance score/fitness, etc.), the CheckMate-648 and Keynote-590 trials indicate that approximately half of these 1,956 patients (~978) achieve a CPS score of ≥10 and, thus, are eligible for treatment with pembrolizumab plus chemotherapy.[4,5] The NHSE clinical expert's figure of 100 patients with OSCC treated with pembrolizumab plus chemotherapy falls short of the estimate of eligible patients and indicates that chemotherapy would be the most relevant comparator for this appraisal.

This shortfall in expected uptake of pembrolizumab with chemotherapy compared to the actual eligible population suggests that there is a significant number of otherwise eligible patients who do not receive immunotherapy. The reason(s) for this are open to question and are discussed below.

Challenges with biomarker testing in clinical practice are preventing access to effective treatment options, impacting patients and adding burden to the NHS

The current recommendation that nivolumab is "recommended only if pembrolizumab plus chemotherapy is not suitable" obligates clinicians to perform two biomarker tests to access treatment, as stated in the Blueteq form for interim funding of this indication.[6] Clinical experts consulted as part of this response have stated that this wording will be problematic when applied in real-world clinical practice. The reasons for this have been outlined below.

Impact on patients and burden on NHS

Delay to initiation of combined IO-chemo treatment

The wording, "*recommended only if pembrolizumab plus chemotherapy is not suitable*", implies sequential testing. This may cause delays in access to treatment as patients will have to have a CPS and TC score to be able to receive nivolumab, increasing the burden on pathologists and clinicians. The end-to-end process of CPS testing (order of the test to receipt of the result) is more complicated than TC testing. TC testing is more readily available and can be performed locally with faster turnaround times. If only this test is required for treatment with nivolumab then it will mean patients will be able to access treatment with nivolumab in a timely manner.

Clinical experts have voiced concerns regarding the turnaround time of CPS testing and would anticipate that most patients will experience a delay of around three weeks until results are received. This is especially important in this population with advanced disease since any delay in initiating treatment may impact their long-term outcomes.

Complexities in testing can introduce unnecessary burden on pathology departments

Dual testing (be it sequential or in parallel) as opposed to PD-L1 TC testing only, per the MHRA license for nivolumab Dual testing (be it sequential or in parallel) as opposed to PD-L1 TC testing only, per the MHRA licence for nivolumab in this indication,7 introduces unnecessary complexity. In practice, establishing eligibility for nivolumab plus chemotherapy under the proposed reimbursement criteria would require that both assays are performed on the tumour tissue specimen. As CPS testing has a different scoring methodology which requires more specialist expertise than PD-L1 TC, this cannot be as easily performed in-house. As both tests will likely need to be undertaken in order to prescribe nivolumab plus chemotherapy treatment, this will increase the burden on pathology departments, essentially doubling the assay requirements for each patient.

The PD-L1 IHC assays are companion diagnostics and therefore the assay that was used in the trial should be used to determine eligibility for their respective therapy. The

current recommendation for nivolumab and its implication of sequential testing is likely to further strain an already pressured testing environment. The potential, highly unfavourable, outcome is the delay in patients starting combined immunotherapy-chemotherapy treatment.

Conclusion

The proposed recommendation for nivolumab plus chemotherapy for patients with first-line OSCC should not be limited to those unsuitable for pembrolizumab. As stated above, pembrolizumab is not yet standard of care in 1L OSCC patients with CPS ≥10 with most patients still receiving chemotherapy. Nivolumab has demonstrated that it is a cost-effective use of NHS resources in these patients when compared to chemotherapy and therefore should be made available for all first-line OSCC patients with PD-L1 TC ≥1.

Furthermore, the additional burden caused by sequential testing of CPS and TC score to identify patients suitable for nivolumab under the current recommendation may delay patients' access to effective treatment options and add significant burden to the NHS, particularly over-stretched pathology departments.

Therefore, the recommendation should allow prescribers to decide which treatment option will be most suitable for their patients and not delay access to treatment. Accordingly, alternative wording options may include:

- *"It is recommended where pembrolizumab plus chemotherapy is not suitable, or where access to CPS testing will delay combined treatment with immunotherapy"*
- *"It is recommended where pembrolizumab is not suitable or if a CPS test result is not readily available"*

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The committee recognised that patients and clinicians would welcome a new effective treatment for untreated adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma as currently these patients have a poor prognosis which has a significant impact on their quality of life.

5. References

1. National Institute for Health and Care Excellence. Appraisal consultation document - Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma [ID2712]. 2022 [accessed 07/10/2022].
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3. National Institute for Health and Care Excellence. Resource impact template: Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). 2021. Available at: https://www.nice.org.uk/guidance/ta737/resources/resource-impact-template-excel-9263083501 [Accessed 01/11/2022].
4. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022;386(5):449-62.
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6. NHS England. National Cancer Drugs Fund List ver1.236 (page 25). 2022. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.236.pdf [Accessed 01/11/2022].
7. Medicines and Healthcare products Regulatory Agency. Summary of Product Characteristics - OPDIVO 10 mg/mL concentrate for solution for infusion. 2022. Available at: https://mhraproducts4853.blob.core.windows.net/docs/bbf7c1c30db8bc259f2f370e757ec51892be05bd [Accessed 01/11/2022].

NICE National Institute for Health and Care Excellence

Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma cancer [ID2712]

Consultation on the appraisal consultation document – deadline for comments 5pm on 1 November 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma cancer [ID2712]

Consultation on the appraisal consultation document – deadline for comments 5pm on 1 November 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
1	This assessment means that patients with squamous oesophageal cancer could have delayed access to effective treatment with nivolumab because of waiting for test results for PD-L1. There is already a minimum two-week delay for centres (the majority) who do not test in-house for PD-L1. As this assessment means that CPS will be tested before TPS and this is unlikely to be done at the same time due to the cost of the test, if CPS is not positive, then there will be another wait of two weeks for TPS results. Patients with oesophageal squamous cancer are unwell and symptomatic of their disease with poor nutrition due to a blocked oesophagus. Even though chemotherapy can be started before PD-L1 results are known, this OSCC responds poorly to chemotherapy alone. Waiting four weeks for a treatment (nivolumab) which can improve response rates, nutrition and survival is unnecessarily long and some patients may fail to benefit from their chemotherapy alone and possibly stop treatment whilst waiting for these results.
2	Secondly, for patients with OSCC, there is often very little tumour in the diagnostic biopsy, and it is likely that a significant number of patients will have insufficient tissue available for a second PD-L1 test. In this case some oncologists may chose not to treat with immunotherapy, or, in the alternative a patient may have a second invasive biopsy (with risks) followed by a further wait for test results.
3	As discussed in the appraisal, in my view it is fundamentally incorrect to compare nivolumab-chemotherapy with pembrolizumab-chemotherapy as the intention of the CheckMate 648 trial was to compare the combination with chemotherapy. Chemotherapy and pembrolizumab has not yet been firmly established as a standard of care, because access to and visibility of PD-L1 testing has been challenging. The committee goes on to note that "there was uncertainty about the comparability of the 2 trials used in the ITC." which supports this argument.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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NICE National Institute for Health and Care Excellence

Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma cancer [ID2712]

Consultation on the appraisal consultation document – deadline for comments 5pm on 1 November 2022. Please submit via NICE Docs.

- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	Does not represent an organisation
Location	
Conflict	No
Notes	

Comments on the ACD: - comment on section 3.3 Suitability of nivolumab and pembrolizumab is assessed using different tests for PD-L1 status

As a GI molecular pathologist currently involved in setting up PDL1 testing pathways, the current proposal will significantly add to the complexity and workload when we are already struggling to provide a core diagnostic service. RCPath have shown that only 3% of pathology departments are adequately staffed at the present time. It would be more deliverable to have a single test based on tumour type e.g. TPS >1% for Nivo rather than requiring a two stage approach of CPS then TPS. We use the 22C3 clone for Pembro decisions scored by CPS and would then need to restain with 28.8 clone for Nivo and score by TPS. This doubles the cost of the testing and the resources required. Testing will almost certainly happen sequentially as we do not have capacity to test both upfront unless these tests are to be centrally commissioned with new money and resources flowing through (though we still need to generate additional staffing even if funded). TPS for Nivo would therefore be delayed if it follows CPS for Pembro. TPS is less labour intensive to score than CPS. From a lab perspective, keeping the pathway simple and avoiding duplication of testing will ensure that test results are available at the right time. Performing two separate tests (different antibodies and different scoring systems) risks this pathway failing in my opinion.

Name	[redacted]
Role	
Other role	
Organisation	Does not represent an organisation
Location	
Conflict	No
Notes	

Comments on the ACD:

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Yes, they are

Has all of the relevant evidence been taken into account?

"Yes, it has been
It would be recommended to take in CHECKMATE data in adenocarcinoma where Nivolumab was used as a 3 weekly regimen to assess the safety and efficacy of 3 weekly schedule. This is necessary as most centres in UK offering chemotherapy

to patients with advanced oesophageal SCC will do so as a 3 weekly Oxaliplatin + Fluoromyridine combination and hence restricting the guidance to 2/4weekly Nivolumab will create significant issues with treatment delivery."

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not think that it is helpful to say that the combination of Nivolumab and chemo can be used for patients where Pembrolizumab combination is not suitable. Clinicians should have the freedom to choose which regimen they seem best fit for their patients if NICE committee feels that both treatments are effective in this disease area.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

United Kingdom & Ireland Oesophagogastric Cancer Group

1st November 2022

To whom in concerns re NICE TA 10572,

We are writing on behalf of the UK and Ireland Oesophagogastric Cancer Group (UKIOG) which is a newly established umbrella group representing oncologists, surgeons, gastroenterologists, and all other medical and non-medical staff involved in the care of patients with oesophageal cancer.

We are concerned that the new NICE guidance on nivolumab for advanced oesophageal squamous cancer may disadvantage patients for several reasons. The proposed guidance suggests that patients are tested for PD-L1 using both CPS and TPS scoring systems and that only patients who have PD-L1 CPS score of <10 but are TPS >1% will be eligible for nivolumab.

Currently, only seven centres in the country offer PD-L1 CPS testing and as a result, most patients have PD-L1 requested externally. This can take two weeks or more to result. As patients with oesophageal squamous cancer often present with advanced disease and nutritional deficiency due to dysphagia being able to start the most effective treatment early is critical. Tumour response to treatment enables better nutrition and avoids the need for invasive treatments such as stents or tubes for feeding. In CheckMate 648 chemotherapy alone was associated with response rates of 20%, and this was more than doubled to 53% by the addition of nivolumab. As chemotherapy with nivolumab cannot be started until PD-L1 CPS and TPS status is known, introducing a significant delay in improved response rates will have a knock-on effect on patient wellbeing, and there is no doubt that some patients who need a quick response will be disadvantaged by this approach. In contrast, PD-L1 TPS scoring is much less specialised than PD-L1 CPS scoring and could likely be done “in-house” for most trusts, giving patients a result in a day or two and not delaying the institution of the most effective treatment.

Secondly, the requirement for PD-L1 testing for both CPS and TPS introduces a significant risk that patients may not have sufficient tissue for both tests. Oesophageal squamous cancer is a tumour which often has scanty cells present on diagnostic biopsy. After testing one PD-L1 assay, there may be insufficient tissue available for a second. If this occurs, the patient will be ineligible for immunotherapy unless a second, invasive biopsy is performed. Endoscopy and biopsy is an invasive procedure which carries a small but non-negligible risk of aspiration, perforation and death. Furthermore, endoscopy waiting lists are a week or two even for cancer referrals, thus introducing even more potential delays into the patient receiving effective therapy.

Finally, we disagree with the model used to compare chemotherapy and nivolumab with standard of care in the NICE assessment. In the CheckMate 648 trial, nivolumab plus chemotherapy showed a survival benefit compared to chemotherapy alone. In the NICE assessment, nivolumab plus chemotherapy was compared not to chemotherapy alone but with chemotherapy plus pembrolizumab which is not the correct comparator. Chemotherapy plus pembrolizumab is not universally adopted thus far as a standard of care, partly due to the challenges associated with PD-L1 CPS testing as discussed above. The CheckMate 648 trial which established nivolumab completed very slightly after the study which established pembrolizumab in this setting (KEYNOTE 590), but it seems that the earlier trial (KEYNOTE 590) has now moved the bar for marginally later studies which were

conducted in good faith. If this is the case, then it seems that later trials will never add value or be assessed fairly by NICE, which could lead to fewer trials and new treatments being delivered for patient benefit.

In summary, we as an organisation would respectfully reconsider the current recommendation for PD-L1 testing in advanced oesophageal squamous cancer with respect to nivolumab. For patients to achieve safe and timely access to immune checkpoint inhibitors, we recommend that nivolumab is made achievable using the criteria established in the landmark CheckMate 648 trial.

Your sincerely

_____

Professor xxxxxxx on behalf UKIOG