**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Nivolumab for treating resected high-risk invasive urothelial cancer ID2694**

**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 1: the draft remit**

| Section | Consultee/ Commentator | Comments | Action |
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| Wording | Bristol-Myers Squibb | No comment. | Response noted. No action required. |
| Timing Issues | Bristol-Myers Squibb | It is important that NICE provides a recommendation for the use of nivolumab in adjuvant treatment of resected high-risk invasive urothelial cancer as close to the time of the marketing authorisation as possible, given the limited effective treatment options currently available to these patients, thus demonstrating an unmet need in this area. | Comment noted. The aim of the STA process is to provide guidance close to the MA being granted. No action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments | Action |
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| Background information | Bristol-Myers Squibb | In paragraph one, it is stated that “Urothelial cancer is most common in the bladder”. This is true; however, it can also originate in the upper urinary tract (renal pelvis or ureter), and these patients were also | Comments noted. The scope has been updated to note that urothelial cancer can also originate in the upper |

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| | | included in the CM274 trial. Therefore, we believe it is important to highlight this patient population too in the background.<br><br>In paragraph 3, it states “People with muscle invasive urothelial cancer may have surgery and/or radiotherapy”. Following clinical consultation, we understand patients either receive surgery or radiotherapy with curative intent. If a patient later progresses after radiotherapy, they can receive salvage cystectomy.<br><br>It should also be noted that this appraisal is intended to assess nivolumab as an adjuvant therapy. Paragraph 3, while relevant, provides substantial focus on the post-relapse treatment pathway and may cause confusion regarding where in the treatment pathway nivolumab will be assessed. We suggest reducing this to make it clear that this is an appraisal for adjuvant therapy. | urinary tract (renal pelvis or ureter). The draft scope has also been updated to note that people with the condition either may receive surgery **or** radiotherapy. No further changes to the scope needed as subsequent treatment lines are relevant to the appraisal. |
| The technology/ intervention | Bristol-Myers Squibb | Yes | Response noted. |
| Population | Bristol-Myers Squibb | The population is not appropriately defined as it excludes patients that did receive neoadjuvant cisplatin chemotherapy (which is a population that was included in the CM274 trial). The population should read as:<br><br>People with invasive urothelial cancer who are at high-risk of recurrence after undergoing radical surgical resection | Comment noted. The population in the draft scope has been changed to reflect the comment. |
| Comparators | Bristol-Myers Squibb | Following clinical consultation, the understanding is that best supportive care is the predominant therapy in the adjuvant setting. | Comment noted. The comparators listed in the scope remain unchanged as: |

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| | | | • Adjuvant chemotherapy (e.g. cisplatin-based regimen)<br>• Best supportive care (monitoring and further treatment at recurrence)<br>This is because for some people, adjuvant chemotherapy is an option. No changes to the scope required. |
| Outcomes | Bristol-Myers Squibb | Yes | Response noted. |
| Economic analysis | Bristol-Myers Squibb | No comment. | Response noted. |
| Equality | Bristol-Myers Squibb | No comment. | Response noted. |
| Other considerations | Bristol-Myers Squibb | Subgroups will be explored if appropriate | Comment noted. No action required. |
| Innovation | Bristol-Myers Squibb | BMS clinical trials have demonstrated that nivolumab is an innovative medicine that has proven its efficacy across multiple indications. Nivolumab can also be considered innovative in the treatment of resected high-risk invasive urothelial cancer, due to its novel | Comments noted. Where relevant and appropriate, the extent to which the technology may be innovative |

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| | | mechanism of action in this therapeutic area. It also offers the potential to make a significant impact on the substantial unmet need, including a long-term remission for a proportion of the target population.<br><br>Nivolumab is a novel immunotherapy agent for the treatment of cancer, with a new mechanism of action as a highly specific programmed death-1 (PD-1) immune checkpoint inhibitor. It specifically binds to PD-1 receptor on the surface of immune cells and restores T-cell activity by blocking the binding of the PD-L1 and PD-L2 ligands found at the tumour site to PD-1 receptors on immune cells. This approach, enabling the body's own immune system to target cancer, is novel in urothelial cancer and is viewed by physicians and patient interest groups as a 'step-change' in its management.<br><br>Based on available data relating to nivolumab, this treatment is of major interest to public health, in particular from the view point of therapeutic innovation, as it has the potential to offer an alternative therapeutic option with an expected significant benefit over management of patients in the absence of nivolumab, including the potential for significantly improved long-term survival in a proportion of patients. | will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required. |
| Questions for consultation | Bristol-Myers Squibb | **Have all relevant comparators for nivolumab been included in the scope?**<br>Yes<br><br>**Are the outcomes listed appropriate?**<br>Yes. DFS is a relevant endpoint in this disease area given the low risk of disease-related death prior to relapse. | Comments noted. No action required. |

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| | | **How is high-risk muscle invasive urothelial cancer defined in clinical practice?**<br>No comments<br><br>**Are there any other subgroups of people in whom nivolumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?**<br>The efficacy of nivolumab appears to be consistent across the majority of subgroups.<br><br>**Where do you consider nivolumab will fit into the existing NICE pathway, Bladder cancer'?**<br><br>As previously discussed, nivolumab will be used as an [redacted]<br><br>**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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:**<br>• **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which nivolumab will be licensed;**<br><br>• **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider** | |

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| | | **population, e.g. by making it more difficult in practice for a specific group to access the technology;**<br><br>• **could have any adverse impact on people with a particular disability or disabilities.**<br><br>**Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.**<br><br>**Age:** As noted in the draft scope, the incidence of invasive urothelial carcinoma is strongly correlated to age. These patients may experience poorer outcomes and more patients may not receive neoadjuvant therapy and adjuvant therapy due to their reduced ability to tolerate chemotherapy. Nivolumab provides a treatment option with proven efficacy and tolerability, with the potential to delay relapse and improve survival.<br><br>**Gender:** As noted in the draft scope, 73% of bladder cancer cases in the UK occur in males. Given the extremely poor outcomes in this patient population, the gender imbalance in diagnoses should be acknowledged.<br><br>**Do you consider nivolumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**<br><br>No further comments. | |

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| | | **Do you consider that the use of nivolumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br><br>**Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.**<br><br>Patients with urothelial carcinoma have significant unmet need: there are few effective therapies, short survival and poor prognosis. However, outcomes can be improved by successful resection. Adjuvant treatment with nivolumab following resection is demonstrated to improve outcomes and reduce the rate of relapse. Although these effects will be demonstrated in the cost-effectiveness modelling, it should be noted that reducing the rate of relapse helps improve quality of life in ways that may not be identified through standard elicitation methods.<br><br>As an additional benefit during the Covid-19 pandemic, avoidance and/or delay of relapse helps patients avoid hospital stays and appointments, preventing possible Covid-19 transmission and alleviating pressure on the NHS.<br><br>**To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.**<br>None | |