National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	Bristol-Myers Squibb	The remit in the draft scope does not reflect the proposed indication submitted to the regulatory authorities. BMS suggest: To appraise the clinical and cost effectiveness of nivolumab with ipilimumab (NIVO+IPI) within its marketing authorisation [redacted].	Comment noted. The remit has been revised to reflect the use in previously treated patients. The wording has been kept broad to allow further changes in the marketing authorisation wording.
Timing Issues	Bristol-Myers Squibb	There is significant unmet medical need in this patient population. Patients with mCRC who have received prior therapy have a very poor prognosis. Limited treatment options are currently recommended by NICE for patients with mCRC that has progressed following initial therapy. Further, there are no therapies recommended by NICE for mCRC patients who are MSI-high, where outcomes may be worse than in patients who are microsatellite stable (MSS).	Comment noted. The remit has been revised to reflect the proposed indication.

Section	Consultee/ Commentator	Comments	Action
		References were provided but are not replicated here.	
Additional comments on the draft remit	Bristol-Myers Squibb	None	Comment noted

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Bristol-Myers Squibb	The background section is not complete and BMS recommends adding the following context. The evidence is uncertain. Patients with MSI-H CRC may have a better prognosis than those who have low levels of MSI during early disease stages;[7] however, this benefit is not observed in patients with metastatic disease, with several studies reporting poorer outcomes. When discussing testing of patients for MSI or MMR proteins, it should also be noted that NICE Guideline 151 [NG151] notes that testing for deficient DNA mismatch repair may inform systemic therapy choices for those with non-metastatic colorectal cancer, but the NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer already recommends such testing for all people with colorectal cancer when first diagnosed. For this reason no further recommendations were made about testing for dMMR.	Comment noted. The background information has been amended to add further information and outcomes for people with metastatic colorectal cancer with high microsatellite instability. Given that the remit is metastatic colorectal cancer, information specific to non-metastatic disease has not been included in the scope. Testing recommendations for

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		References were provided but are not replicated here.	dMMR in the entire mCRC population (as per DG27) are listed in the background section.
	Promega UK Ltd	For the subsection entitled "Microsatellite Instability", consideration should be given to further specifying highly sensitive markers for detecting MSI in colorectal tumours. Accurate identification of MSI-H patients is critical to the effectiveness of nivolumab with ipilimumab in this population. A recent panel of experts from the European Society of Medical Oncology (ESMO) developed a set of recommendations for assessing mismatch repair status of solid tumours in patients being considered for immunotherapy (1). This expert panel recognized that traditional molecular testing based on PCR amplification of microsatellite markers is typically performed via one of two marker panels: one using a mixture of mononucleotide and dinucleotide repeats (i.e., the Bethesda panel BAT25, BAT26, D5S346, D2S123, D17S250), and the other using a five poly-A mononucleotide repeats (BAT25, BAT26, NR21, NR24, NR27). It was noted the five poly-A panel is recommended given its higher sensitivity and specificity. Both panels have been and are being used to assess MSI in immunotherapy clinical trials (2-9). The markers BAT25 and BAT26 are common to both panels and have been well-established as highly sensitive for detecting microsatellite instability in colorectal cancers as well as across genetically diverse human populations due to their quasimonomorphic nature (10). Promega would therefore recommend additional detail to be included in the scope along the following lines: "MSI status is determined by PCR (polymerase chain reaction)-based analysis of tissue samples from colorectal cancer tumours to detect a standardised panel of DNA markers, *including BAT25 and BAT26*."	Comment noted. The background section aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. Where relevant, details on identification and diagnosis of the condition may be considered and explored during the appraisal process. No change to scope required.

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		In the last 5-7 years, MSI tests based on NGS technology have been developed for characterisation of solid tumours. However, NGS-based MSI tests are not standardised and vary significantly in terms of the library preparation tools used, target capture enrichment strategy, number and type of microsatellite loci analysed, algorithms used for MSI scoring, and thresholds established for MSI-H status determination (11,12). All NGS approaches have been developed based on MSI by PCR-based testing outcomes. MSI by PCR is used to identify MSI-H and MSS patients prior to NGS MSI testing, and or to adjust or train algorithms to yield the same results as the MSI by PCR loci. Therefore, caution should be exercised in recommending NGS MSI testing for routine clinical use at this particular point in time.	
Population	Bristol-Myers Squibb	BMS does not believe that the proposed population of this appraisal is appropriate. This does not reflect the population of patients described in the proposed indication: [redacted].	Comment noted. The population has been revised to reflect use in previously treated patients. The wording has been kept broad to allow further changes in the marketing authorisation wording.
Comparators	Bristol-Myers Squibb	The proposed indication is [redacted]. Thus, first-line treatments listed in the scope will not be relevant comparators for the purposes of this STA.[10, 11] We also note that certain comparators, such as single-agent irinotecan, are rarely used in clinical practice and therefore may not be relevant to compare to. Clinical validation will be conducted to ensure that the comparators included are in line with UK clinical practice.	Thank you for your comment. The scope has been revised to remove first-line treatments. According to NICE's method guide, all potentially relevant

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			comparators should be identified. Therefore, irinotecan remains a comparator.
Outcomes	Bristol-Myers Squibb	No further comments.	Comment noted.
Economic analysis	Bristol-Myers Squibb	BMS do not agree with the following statement "The economic modelling should include the costs associated with diagnostic testing for microsatellite instability status in people with metastatic colorectal cancer who would not otherwise have been tested". As noted in the draft scope, current NICE guidance recommends that all people with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry for mismatch repair proteins or MSI testing to identify tumours with dMMR.11, 12 This was based on economic evaluations conducted as part of Diagnostics Guidance 27 [DG27].12 Further, NG151 notes that testing for dMMR may inform systemic therapy choices for those with non-metastatic colorectal cancer, but the NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer already recommends such testing for all people with colorectal cancer when first diagnosed.8 For this reason no further recommendations were made about testing for deficient DNA mismatch repair. Based on this NICE guidance, all patients will be offered testing for MSI and dMMR, regardless of NIVO+IPI availability. As noted in NG151, testing for dMMR may inform systemic therapy choices for those with non-metastatic colorectal cancer. Hence, MSI testing has the potential to impact on usage of	Thank you for your comment. Where relevant, identification and diagnosis of the condition and the implications of that for the economic modelling may be considered by the committee during the appraisal process. No change has been made to the scope.

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		several components of the treatment pathway, predominantly adjuvant treatment with 5-FU,13-15 rather than NIVO+IPI use only. Further, it should be noted that patients will be tested on first diagnosis, in line with NICE guidance. Based on the proposed indication, NIVO+IPI will be available for the treatment of mCRC. However, approximately 56% of patients with CRC diagnosed in the UK are diagnosed stage II or III, and it is estimated that only 55% of these patients progress to mCRC.11 As such, a large proportion of patients will receive MSI testing at diagnosis, but will not receive NIVO+IPI until substantially later, provided that patients reflect the proposed indication. It is not feasible to accurately or appropriately model this interim period. Additionally, it is inappropriate to assume that MSI testing is undertaken immediately prior to NIVO+IPI, as a large proportion of these patients may die prior to receiving NIVO+IPI (for example, while receiving first-line therapy for mCRC). In summary, as per NICE guidance, all patients should now be tested across the UK.12 Therefore, we believe that the appropriate economic analysis for this STA should be that of NIVO+IPI itself, excluding diagnostic test costs.	
	Promega UK Ltd	The economic modelling should consider using performance characteristics for diagnostic testing for microsatellite instability status of assays that are currently CE-IVD marked for in vitro diagnostic use. Assessment of sensitivity of MSI PCR assays vary widely in literature and are dependent on microsatellite regions interrogated, reference standard used, tissue and cancer type, as well as assay-specific criteria such as base pair shift cut-offs for individual microsatellite loci calling and MSI-H threshold. Given these multi-variate factors, performance is reported as a range based on evaluation and interpretation across numerous studies. It is therefore recommended to rely on standardised procedures in performance evaluation of in vitro diagnostic assays for performance characteristics to inform the economic modelling.	Comment noted. Where relevant, identification and diagnosis of the condition and the implications of that for the economic modelling may be considered by the committee during the appraisal process. No changes have been made to the scope.

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		Accurate identification of MSI-H patients is critical to evaluate the cost-effectiveness of nivolumab with ipilimumab in this population. Recent evidence suggests that up to 10% of patients enrolled in immunotherapy trials may have an incorrect MSI status which could lead to treatment resistance for patients and unnecessary cost burden for healthcare systems (13). Due to the comparatively low cost of diagnostic testing compared to immunotherapy treatment, there is growing support for diagnostic approaches that improve MSI status determination, mainly the use of both immunohistochemistry (IHC) for mismatch repair protein expression and MSI by PCR for patient eligibility for immunotherapy. It is therefore recommended to include in cost effectiveness analysis the impact of use of one diagnostic approach (with 10% false accuracy rate) with the cost effectiveness approach of an approach using both IHC and PCR analysis, which is known to yield near 100% sensitivity and specificity for MSI status (14).	
Equality and Diversity	Bristol-Myers Squibb	No equality issues have been identified.	Comment noted
Other considerations	Bristol-Myers Squibb	CheckMate 142 did not assess a subgroup of patients with RAS wild-type colorectal cancer and thus a subgroup analysis is not possible.	Comment noted. The subgroup has been removed from the scope.
Innovation	Bristol-Myers Squibb	BMS consider NIVO+IPI to be innovative in the treatment of adults with dMMR or MSI-H metastatic colorectal cancer, due to the novel mechanism of action in this therapeutic area and the potential for it to make a significant impact in a patient population with a substantial unmet need.	Comment noted. The extent to which the technology may or may not be innovative will be considered in any appraisal of the

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		Nivolumab is 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 colorectal cancer and is viewed by physicians and patient interest groups as a 'step-change' in its management. Ipilimumab (Yervoy), is a fully human monoclonal, immunoglobulin G1-κ antibody (IgG1 HuMAb) that acts as a Cytotoxic T-lymphocyte antigen-4 (CTLA4) checkpoint-inhibitor, blocking the interaction of CTL-4 receptor with its costimulatory ligand B7 (CD80 (B7-1) and CD86 (B7-2)). This results in T-cell potentiation due to blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction, resulting in T-cell activation, proliferation, and lymphocyte infiltration into tumours, which leads to tumour cell death. Checkpoint inhibitors such as nivolumab and ipilimumab demonstrate significant clinical activities and survival benefits in cancer immunotherapy, both as a monotherapy and as combination therapies with other immunotherapies or conventional chemotherapies. In patients with advanced or recurrent colorectal cancer, outcomes are poor, with very short survival and few recommended treatment options. Further, there are no therapies recommended by NICE for mCRC patients who have microsatellite instability (MSI), where outcomes may be worse than in patients who are microsatellite stable (MSS). Thus, there is significant unmet need in this patient population. Based on available data relating to NIVO+IPI, this is of major interest for public health, in particular from the view point of therapeutic innovation, as it	technology. No action required.

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		has the potential to offer an alternative therapeutic option with an expected improved significant benefit over management of patients in the absence of nivolumab. *References were provided but are not replicated here.*	
Questions for consultation	Bristol-Myers Squibb	**1. Have all relevant comparators for nivolumab with ipilimumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for recurrent or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency?** FOLFOX and FOLFIRI can be used interchangeably in colorectal cancer treatment. In addition, some of the comparators listed, e.g. single agent irinotecan, are so rarely used in UK clinical practice. Chemotherapy is the only treatment available to these patients at the moment.	Comment noted. FOLFOX has been added as a comparator. According to NICE's method guide, all potentially relevant comparators should be identified. Therefore, irinotecan remains a comparator.
	Bristol-Myers Squibb	**2. Are there any other subgroups of people in whom NIVO+IPI is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No. BMS do not believe there exist currently any subgroups which should be examined separately.	Comment noted.
	Bristol-Myers Squibb	**3. Where do you consider NIVO+IPI will fit into the existing NICE pathway?** In line with the proposed indication submitted to the regulatory authorities, use of [redacted]	Comment noted. The scope has been updated to reflect the proposed indication.

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		[redacted], and is thus considered as second-line and subsequent treatment option	
	Bristol-Myers Squibb	**4. Which treatments are considered to be established clinical practice in the NHS for recurrent or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency?** No specific NICE guidance exists for patients with dMMR/MSI-H and treatment options are based on the overall mCRC population.	Comment noted.
	Bristol-Myers Squibb	**5. Do you consider that the use of nivolumab with ipilimumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** There are several key benefits of NIVO+IPI that may not be captured in the economic model by the utility and quality adjusted life year (QALY) assessment. In comparison with chemotherapy, NIVO+IPI has improved tolerability, which can potentially help maintain patient dignity and facilitate normal life, as well as enabling patients to spend less time in hospital. Further, as there are few efficacious therapies with a manageable safety profile, NIVO+IPI provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving only BSC due to treatment history and limited alternative options, which would manage the patient's symptoms, but with limited impact on survival. Due to its unique mode of action, nivolumab is associated with durable responses, increased efficacy, improved tolerability and prolonged survival benefit all of which improve the patient quality of life. This is consistent with evidence reported across other cancer indications with longer follow-up including advanced non-small cell lung cancer, renal cell carcinoma and melanoma[19]	Comment noted.
	Bristol-Myers Squibb	**6. 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.**	Comment noted.

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		BMS do not consider there to be any barriers to the adoption of NIVO+IPI into UK clinical practice.	
	Bristol-Myers Squibb	**7. Would it be appropriate to use the cost comparison methodology for this topic?** BMS do not believe that it would be appropriate to undertake a cost comparison, as NIVO+IPI provides a clear benefit in survival in this indication.	Comment noted.
	Bristol-Myers Squibb	**8. Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** As mentioned in our response to question 2, no specific NICE guidance exists for patients with dMMR/MSI-H and treatment options are based on the overall mCRC population. The availability of NIVO+IPI would provide a treatment option that targets a specific biomarker, which currently represents an unmet need in the treatment pathway of patients with dMMR/MSI-H mCRC. Comparator treatments in this indication currently provide a mean overall survival (OS) of 7.7-17.9 months and NIVO+IPI has shown to provide a significant OS benefit compared with current treatment options. Thus, NIVO+IPI is a targeted therapy for a small, molecularly-stratified patient population, allowing clinicians to make an informed treatment decision and avoid inefficient resource utilisation due to selection of other poorly performing treatments.	Comment noted.
	Bristol-Myers Squibb	**9. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** The primary endpoint driving the model for the comparators is OS, which is considered clinically relevant.	Comment noted.
	Bristol-Myers Squibb	**10. Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** For this submission, a systematic literature review will be conducted to identify all evidence in relation to the clinical effectiveness of the intervention	Comment noted.

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		and relevant comparators this indication. However, BMS are not aware of any ongoing trials for the current list of comparators (reporting next year).	
Additional comments on the draft scope	Bristol-Myers Squibb	None	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope