**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]**

**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 [sic] | Action |
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| Wording | Merck Sharp & Dohme | The wording seems appropriate. | Thank you for your comment. No action required. |
| Timing Issues | Merck Sharp & Dohme | We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval. | Thank you for your comment. No action required. |
| Additional comments on the draft remit | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |
| | Promega | 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 pembrolizumab 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. The poly-A panel was used in the Keynote-016, -059 and in confirmatory testing in the Keynote-158 trials for pembrolizumab (2-7). 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 (8). 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.***" | Thank you for your comment. 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 (9,10). 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. | |
| The technology/ intervention | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |
| Population | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |
| Comparators | Merck Sharp & Dohme | MSD would like to point out that:<br>• Tegafur with uracil (in combination with folinic acid), while recommended as an option in the old NICE CG131 guideline (now replaced by NICE NG151), is not a relevant comparator for this appraisal as this regimen is no longer available in the UK.<br>• Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable), while recommended as an option in the old NICE CG131 guideline (now replaced by NICE NG151), is not a relevant comparator for this appraisal as this is only very rarely used in UK clinical practice.<br>• Capecitabine is not a relevant comparator for this appraisal as it is used in elderly and frail patients who have a poor performance status (PS). | Thank you for your comments.<br>Tegafur with uracil (in combination with folinic acid) is recommended in NICE TA61. Keep in as comparator, no change needed. |

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| | | MSD intends to conduct clinician interviews to understand current clinical practice in the UK and determine if this is still the case.<br>• Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) should be included as a relevant comparator for this appraisal as it is commonly used in routine clinical practice for the first-line treatment of metastatic colorectal cancer in the UK. | The recommendations on raltitrexed (NICE TA93) have been withdrawn because its use is established clinical practice, therefore keep in as a comparator. No change needed.<br><br>Oral therapy with capecitabine is recommended as an option for the first-line treatment of metastatic colorectal cancer (NICE TA61). Keep in as comparator, no change needed.<br><br>According to NICE clinical pathway for colorectal cancer and TA439, FOLFIRI in combination with Cetuximab or Panitumumab was recommended for treating previously untreated epidermal growth factor receptor (EGFR)-expressing, |

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| | | | RAS wild-type metastatic colorectal cancer in adults. NICE recognises the need for the scope to be inclusive of all potentially relevant comparators as per the methods guide, and therefore have included FOLFIRI as a potential first line comparator in the scope. |
| Outcomes | Merck Sharp & Dohme | The outcomes listed are appropriate and will capture the most important health-related benefits (and harms) of the technology. | Thank you for your comment. No action required. |
| Economic analysis | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |
| | Promega | 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 | 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 |

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| | | rely on standardised procedures in performance evaluation of *in vitro* diagnostic assays for performance characteristics to inform the economic modelling.<br><br>Accurate identification of MSI-H patients is critical to evaluate the cost-effectiveness of pembrolizumab 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 (11). 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 (12). | the appraisal process. The scope remains unchanged. |
| Equality and Diversity | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |
| Other considerations | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |
| Innovation | Merck Sharp & Dohme | MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits.<br>Pembrolizumab has the potential to improve outcomes for patients with Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) | Thank you for your comment. The extent to which the technology may or may not be |

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| | | Stage IV Colorectal Carcinoma and would represent a step-change in the management of these patients. | innovative will be considered in any appraisal of the technology.<br>No action required. |
| Questions for consultation | Merck Sharp & Dohme | **Question:** Have all relevant comparators for pembrolizumab been included in the scope?<br>**Answer:** MSD would like to point out that:<br>• *Folinic acid plus fluorouracil plus irinotecan (FOLFIRI)* should be included as a relevant comparator for this appraisal as it is commonly used in routine clinical practice for the first-line treatment of metastatic colorectal cancer in the UK.<br>Additionally:<br>• *Tegafur with uracil (in combination with folinic acid)*, while recommended as an option in the old NICE CG131 guideline (now replaced by NICE NG151), is not a relevant comparator for this appraisal as this regimen is no longer available in the UK.<br>• *Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable)*, while recommended as an option in the old NICE CG131 guideline (now replaced by NICE NG151), is not a relevant comparator for this appraisal as this is only very rarely used in UK clinical practice.<br>• *Capecitabine* is not a relevant comparator for this appraisal as it is used in elderly and frail patients who have a poor performance status (PS). MSD intends to conduct clinician interviews to understand current clinical practice in the UK and determine if this is still the case. | Thank you for your comments.<br>According to NICE clinical pathway for colorectal cancer and TA439, FOLFIRI in combination with Cetuximab or Panitumumab was recommended for treating previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults. NICE recognises the need for the scope to be inclusive of all potentially relevant comparators as per the methods guide, and therefore have included |

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| | | **Question:** Which treatments are considered to be established clinical practice in the NHS for untreated colorectal cancer with high microsatellite instability or mismatch repair deficiency?<br>**Answer:** In patients with advanced and metastatic colorectal cancer, one of the following sequences of chemotherapy are used unless contraindicated:<br>• FOLFOX as first-line treatment then single-agent irinotecan as second-line treatment or<br>• FOLFOX as first-line treatment then FOLFIRI as second-line treatment or<br>• CAPOX as first-line treatment then FOLFIRI as second-line treatment<br>For patients with previously untreated EGFR-expressing, RAS wild-type metastatic colorectal cancer in adults, cetuximab is recommended in combination with<br>• FOLFOX or<br>• FOLFIRI<br>Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with<br>• FOLFOX or<br>• FOLFIRI<br><br>**Question:** Are the outcomes listed appropriate?<br>**Answer:** Yes.<br><br>**Question:** Are the subgroups suggested in 'other considerations appropriate? | FOLFIRI as a potential first line comparator in the scope.<br>Tegafur with uracil (in combination with folinic acid) is recommended in NICE TA61. Keep in as comparator, no change needed.<br>The recommendations on raltitrexed (NICE TA93) have been withdrawn because its use is established clinical practice, therefore keep in as a comparator. No change needed.<br>Oral therapy with capecitabine is recommended as an option for the first-line treatment of metastatic colorectal cancer (NICE TA61). Keep in as comparator, no change needed. |

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| | | **Answer:** The subgroup of people with RAS wild-type colorectal cancer suggested in “Other considerations” is appropriate, for comparisons versus cetuximab- or panitumumab-containing regimens where this factor is a treatment effect modifier.<br><br>**Question:** Are there any other subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?<br>**Answer:** MSD does not currently anticipate there will be subgroups of people in whom pembrolizumab will be more clinically effective or cost effective.<br><br>**Question:** Where do you consider pembrolizumab will fit into the existing NICE pathway, Colorectal cancer (2020)?<br>**Answer:** It is anticipated that pembrolizumab will fit under the part of the NICE pathway which refers to “Managing metastatic colorectal cancer”, “First-line biologic therapy” (https://pathways.nice.org.uk/pathways/colorectal-cancer/managing-metastatic-colorectal-cancer#content=view-node%3Anodes-first-line-biological-therapy). If approved, pembrolizumab would be considered as a first-line treatment option for patients with metastatic disease with microsatellite instability-high or mismatch pepair deficiency.<br><br>**Question:** 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: | |

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| | | • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab pembrolizumab will be licensed;<br>• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br>Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.<br>**Answer:** MSD does not think that the proposed remit and scope need to change in order to meet these aims.<br><br>**Question:** Do you consider pembrolizumab 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>**Answer:** Yes, MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits. Pembrolizumab has the potential to improve outcomes for patients with Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma and would represent a step-change in the management of these patients.<br><br>**Question:** Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? | |

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| | | 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>**Answer:** No, MSD does not consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.<br><br>**Question:** 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>**Answer:** No, MSD does not consider that there will be any barriers to adoption of this technology into practice. | |
| Additional comments on the draft scope | Merck Sharp & Dohme | None. | Thank you for your comment. No action required. |

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