National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

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
Wording	BMS	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider].	Thank you. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	The wording seems appropriate.	Thank you. No action required.
Timing Issues	BMS	Malignant pleural mesothelioma (MPM) is a rare, occupational-related lung cancer caused by asbestos exposure. As MPM incidence is related to asbestos exposure over time, and use of asbestos was not banned completely in the UK until 1999, (Mesothelioma UK, 2020) the UK is currently experiencing its peak of expected incident cases of around 10 per 100,000 population. Incidence rates are projected to fall to 3 per 100,000 by 2035 (Cancer Research UK, 2020). Patients with MPM have a poor prognosis, and there is an extremely high unmet need at the current time. There is no innovative immunotherapy	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this

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		approved for use, with little progress in improved survival and no new therapies approved in the last two decades. The current standard-of-care (platinum doublet chemotherapy, PDC) has limited clinical benefit, with most patients surviving less than a year after diagnosis.	topic into its work programme.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	The treatment under consideration has been presented at a peer reviewed international meeting. It is awaiting publication and licencing.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
Additional comments on the draft remit	BMS	None	Noted. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	None	Noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BMS	We request that the occupation-related and preventable nature of the disease is emphasised further in the background information to distinguish MPM from other lung cancers. Unlike other lung cancers, MPM is a preventable, occupation-related disease: 94% of cases in the UK are caused by prior asbestos exposure while at work and it is considered an industrial injury. Due to its association with heavy industry the incidence rates vary across England, with higher rates in areas of heavy industry (e.g., the North East and Southern England) (Cancer Research UK, 2020; NHS England, Standard Contract for Malignant Mesothelioma 2013).	Thank you for your comment. The background section of the scope has been updated to emphasise the occupational and preventable nature of the condition.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	It states the aim of treatment is to reduce tumour size and improve symptoms. This is not reflective of chemotherapy aims. The primary aim is to prolong life expectancy.	Thank you for your comment. The background section of the scope has been updated to reflect the primary aim of chemotherapy to prolong life expectancy.
The technology/ intervention	BMS	Yes [the description of the technology or technologies is accurate].	Thank you. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	Yes [the description of the technology or technologies is accurate].	Thank you. No action required.

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Population	BMS	Yes [the population is defined appropriately].	Thank you. No action required.
	Royal College of Pathologists	The draft scope indicates that if the evidence allows the level of programmed death-ligand1 expression will be considered. If the evidence demonstrates that PD-L1 testing is routinely recommended and level of expression will determine treatment eligibility then the RCPath would need to comment on impact to staff and lab costs. If PD-L1 testing is not required then the RCPath need not comment.	Thank you for your comment. The economic modelling should include the costs associated with PD-L1 testing for this subgroup analysis as PD-L1 testing is not already part of routine testing for people with MPM. No action required.
	British Thoracic Oncology Group	Yes [the population is defined appropriately]. We do not feel that there is sufficient data from this trial to assess outcomes by PDL1 expression. Only 20% of patients were PDL1<1%.	Thank you for your comment. The 'other considerations' section of the scope states that, if the evidence allows, subgroups with PD-L1 expression will be considered. No action required.
Comparators	BMS	The UK National Mesothelioma Audit 2020 reported that 40% of all patients with MPM in England received chemotherapy from 2016-2018, which increased to 58% of patients with a performance status of 0-1 who are recommended to receive chemotherapy. Of those patients who received chemotherapy, pemetrexed with carboplatin was the most common regimen used (48%), followed by pemetrexed with cisplatin (20%). As the standard systemic anticancer therapy used to treat MPM in	Thank you for your comment. At the scoping stage of the appraisal, identification of comparators is inclusive. The Appraisal Committee can consider as

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		the UK, BMS considers pemetrexed with carboplatin or cisplatin the best alternative care and the most appropriate comparator for this appraisal. Raltitrexed is not approved for use in the UK for the first-line treatment of MPM and is not commonly used in the NHS. As such, BMS does not consider raltitrexed to be an appropriate comparator for this appraisal. Best supportive care (BSC) is any type of symptomatic treatment received by patients with MPM, and is the only treatment received by patients who are not fit enough to receive standard chemotherapy. According to the 2018 British Thoracic Society Guidelines, the types of treatment that can be classed as BSC vary and can include standard cancer-related symptom management for breathlessness, pain and fatigue, as well as end-of-life care. The guidelines state there are no studies of symptom control that specifically relate to MPM.	comparators technologies that do not have a marketing authorisation for the indications defined in the scope when they are considered to be part of established clinical practice for this indication in the NHS, please see section 6.2.4 of the NICE methods guide. The exclusion of any comparators from the decision problem in the company submission should be fully justified and will be considered during the course of the appraisal. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	The “real life” NHS standard will be carboplatin and pemetrexed despite what NICE and other guidelines state. Only a proportion receive cisplatin. For logistical and chemo unit chair time reasons, carboplatin is often given instead of cisplatin based on an assumption that the two are equally efficacious. Ralitrexed is essentially not used in the 1st line setting within the UK. This is because there isn’t a definable subgroup of patients who would not be	Thank you for your comment. At the scoping stage of the appraisal, identification of comparators is inclusive. The Appraisal Committee can consider as

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		appropriate for cisplatin pemetrexed but would be appropriate for cisplatin raltitrexed. It is also unlicensed. Best supportive care is not an appropriate comparator because this technology relates to a particular group of fit patients for whom this would not be deemed acceptable unless specifically requested by the patient.	comparators technologies that do not have a marketing authorisation for the indications defined in the scope when they are considered to be part of established clinical practice for this indication in the NHS, please see section 6.2.4 of the NICE methods guide. The exclusion of any comparators from the decision problem in the company submission should be fully justified and will be considered during the course of the appraisal. No action required.
Outcomes	BMS	Yes [the outcome measures capture the most important health related benefits (and harms) of the technology].	Thank you. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	We agree with the outcome measures but feel NICE should be aware of serious limitations is standardising the way mesothelioma is measured on CT scans. There is significant variability in this area. As a result we would	Thank you for your comment. No action required.

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		caution that care be taken when assessing outcomes such as response rate or progression free survival. We feel the overall survival be the key outcome measure to be evaluated as well as toxicity and quality of life.	
Economic analysis	BMS	None	Noted. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	No comment	Noted. No action required.
Equality and Diversity	BMS	BMS is not aware of specific equality issues for this appraisal. However, as MPM is a preventable, occupation-related disease caused by asbestos exposure, BMS wishes to highlight that MPM incidence rates vary across England, with higher rates in areas of heavy industry (e.g., the North East and Southern England). Also, as MPM is a rare cancer, patients may be referred for treatment in the NHS in a limited number of specialist quaternary centres, which may require patients to travel long distances from their home if they live in a rural setting. As patients with MPM are often old and diagnosed at a late stage, they can be too frail to travel for treatment (NHS England, Standard Contract for Malignant Mesothelioma 2013).	Thank you for your comment. The population in the scope is 'Adults with untreated unresectable malignant pleural mesothelioma'. During the appraisal, and in particular when considering subgroup analyses, the committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. No action required.

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	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	We do not envisage any issues relating to protected characteristics in relation to this appraisal.	Thank you for your comment. No action required.
Other considerations	BMS	None	Noted. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	We do not feel that PDL1 expression should be examined as a defined subgroup as the trial was not designed to be statistically robust in this subgroup. Histological subgroups were examined in the trial but we feel NICE should examine epithelioid and non-epithelioid as per the study.	Thank you for your comment. The 'other considerations' section of the scope states that, if the evidence allows, subgroups with PD-L1 expression, epithelioid, sarcomatoid and biphasic histology will be considered. No action required.
Innovation	BMS	There are no innovative immunotherapies approved for use in MPM, with little progress in improved survival and no new therapies approved in the last two decades. The current standard of care (platinum doublet chemotherapy, PDC) has limited clinical benefit, with most patients surviving less than a year after diagnosis.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and

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		CTLA-4 and PD-1 inhibitors have not previously been available to MPM patients outside of a clinical trial setting and will provide a therapy with a new mechanism of action for treating these patients. Nivolumab in combination with ipilimumab has the potential to generate an early response followed by a long-term durable response translating into a clinically significant survival benefit and improved quality of life (including incremental QALY benefit over existing standard of care). CheckMate-743 is the first positive randomised trial of any immunotherapy for the first-line treatment of patients with unresectable MPM. Interim results with a median follow-up of 29.7 months showed a highly significant overall survival (OS) benefit for nivolumab + ipilimumab versus PDC (hazard ratio, 0.74; P = 0.002); 2-year OS rates were 41% versus 27%, respectively. Safety data for nivolumab + ipilimumab show that the dosing and schedule is tolerable in patients with MPM, with an acceptable discontinuation rate due to adverse events.	substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	We believe this is a significant step change in the management of this disease. Cisplatin pemetrexed has been the only treatment licensed in this disease and is based on a trial recruiting patients 2 decades ago. The CHECKMATE 743 trial clearly shows that a non-chemotherapy approach using immunotherapy alone has led to significant survival benefits over standard chemo. The ability to avoid chemotherapy presents a patient with significant toxicity benefits. Chemotherapy is associated with significant risks of myelosuppression and infection. These are not seen with immunotherapy.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation

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		The UK thoracic oncology specialists have become very fluent in managing patients on immunotherapy. There is no doubt that despite the side effect profile of immunotherapy it is significantly less oneous than chemotherapy.	during the assessment. No action required.
Questions for consultation	BMS	*Where do you consider nivolumab with ipilimumab will fit into the existing NICE pathway, Respiratory conditions (2018)?* Nivolumab + ipilimumab would replace pemetrexed + cisplatin (TA135) as the current standard of care for the first-line treatment of unresectable MPM.	Thank you for your comment. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	Where do you consider nivolumab with ipilimumab will fit into the existing NICE pathway, Respiratory conditions (2018)? We feel that nivolumab + ipilimumab will replace cisplatin + pemetrexed as first line standard of care.	Thank you for your comment. No action required.
Additional comments on the draft scope	BMS	None	Noted. No action required.
	Royal College of Pathologists	None	Noted. No action required.
	British Thoracic Oncology Group	None	Noted. No action required.

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

None