National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [ID3757]
Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Bristol Myers Squibb	Appropriate.	Comment noted. No action required.
	British Thoracic Oncology Group	No comment provided	N/A
Wording	Bristol Myers Squibb	Bristol Myers Squibb (BMS) propose changing the wording of 'early' to '[redacted]', and 'chemotherapy' to '[redacted]', in line with the anticipated marketing authorisation wording for CheckMate-816 (CM816): [redacted]	Thank you for your comment. The remit uses 'within it's marketing authorisation' to capture the full indication in line with the marketing authorisation wording. The wording of the remit has been updated

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			to include ‘neoadjuvant’ and ‘resectable’.
	British Thoracic Oncology Group	The wording within the draft remit/appraisal objective paragraph should include the term "neoadjuvant", as in the title.	Thank you for your comment. The wording of the remit has been updated to include ‘neoadjuvant’ and ‘resectable’.
Timing issues	Bristol Myers Squibb	The approval of nivolumab (nivo) + platinum-doublet chemotherapy (PDC) in this indication will introduce systemic immunotherapy-based anticancer treatment earlier in the treatment pathway, resulting in improved pathological complete response and event-free survival for patients, and should therefore be considered a priority.	Comment noted. NICE tries to schedule topics in order to produce timely guidance if possible. No action required.
	British Thoracic Oncology Group	Urgent, as the phase III trial CHECKMATE816 has now been published in the NEJM https://www.nejm.org/doi/10.1056/NEJMoa2202170. The study concluded that in patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherpay alone. The addition of nivolumab to noadjuvant chemotherapy did not increase the incidence of adverse events or impede the feasibility of surgery. Based on the results of this trial, the US FDA has approved its use for selected adult patients with resectable NSCLC. This is a practice changing clinical trial. The magnitude of benefit is greater in stage IIIA disease, in patients with PDL1 expression >1%, and nonsquamous histologic type	Comments noted. No action required.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Bristol Myers Squibb	No comment provided	N/A
	British Thoracic Oncology Group	No	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bristol Myers Squibb	The second paragraph states “NICE guideline Lung cancer: diagnosis and management (NG122) recommend surgery, radiotherapy, chemoradiotherapy or a combination of these for early-stage disease.” BMS propose changing chemoradiotherapy to chemotherapy since chemoradiotherapy is covered by “a combination of these”. In the same paragraph, NLCA data from 2017 are cited. In 2022, the 2019 and 2020 NLCA data have been published[1], which are more appropriate to cite.	Thank you for your comments. The background section of the scope has been updated by changing chemoradiotherapy to chemotherapy. The background section of the scope has also been updated by citing NLCA 2020 data.
	British Thoracic Oncology Group	There is a lack of discussion of phase I-II trials to date of the use of immunotherapy (IO) in this setting. There is no mention of other IO agents that have also been studied	Comment noted. No action required.
The technology/ intervention	Bristol Myers Squibb	This intervention is listed as nivolumab with chemotherapy. BMS propose changing the technology wording to [redacted]	Thank you for your comment. The technology/intervention

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted] as per the anticipated marketing authorisation wording.	section of the scope has been updated to reflect this.
	British Thoracic Oncology Group	Yes	Comment noted. No action required.
Population	Bristol Myers Squibb	The draft scope refers to stage IB-IIIB patients. It is unclear which AJCC edition the stages referenced in the draft scope relate to. In CM816, patients with stage IB-IIIA based on the 7th AJCC edition of cancer staging were enrolled. BMS propose to maintain consistency with the pivotal clinical trial and refer to the population of interest for this appraisal as patients with stage IB-IIIA NSCLC based on the 7th AJCC edition.	Comments noted. The technology will be appraised according to its marketing authorisation. Staging remains as a subgroup as life expectancy and the comparators may differ between stages. The population section has been updated to 'Adults with resectable NSCLC'.
	British Thoracic Oncology Group	No. Population should probably be restricted to up to stage IIIA disease and not include IIIB, because the Phase III CHECKMATE816 trial did not accept Stage IIIB patients, and nor did the key Phase II studies with Nivolumab (NADIM and NEOSTAR).	Comment noted. The technology will be appraised according to its marketing authorisation. Staging remains as a subgroup as life expectancy and the comparators may differ between stages.

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			The population section has been updated to 'Adults with resectable NSCLC'.
Subgroups	Bristol Myers Squibb	No comment provided	N/A
	British Thoracic Oncology Group	No comment provided	N/A
Comparators	Bristol Myers Squibb	**Current draft scope comparators:** • Cisplatin-based PDC • Atezolizumab after adjuvant cisplatin-based PDC (subject to NICE appraisal) **BMS' proposed comparators:** • Surgical resection followed by adjuvant platinum-based PDC • Surgical resection alone **Comparator summary:** People with resectable NSCLC are currently treated with surgical resection followed by four cycles of adjuvant PDC (if tolerable) in the UK. BMS consider either surgical resection followed by adjuvant PDC or surgical resection alone to be the most relevant comparators for this appraisal. BMS provide evidence for the suitability of either cisplatin-based or carboplatin-based PDC as a comparator, as opposed to a cisplatin-based PDC comparator alone, in section 1.	Thank you for your comments. The comparators in the scope have been updated. NICE's updated 'Process and methods' guide highlights that 'the scope identifies all potentially relevant comparators that are established practice in the NHS. It considers issues likely to be discussed by the committee when selecting the most appropriate comparator. At this stage of the

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		BMS do not consider adjuvant atezolizumab a relevant comparator for this appraisal. BMS provide evidence for a lack of comparability between neoadjuvant nivo+PDC and adjuvant atezolizumab in section 2. **1. Platinum-based chemotherapy:** In CM816, a platinum-based combination of either vinorelbine, gemcitabine, docetaxel, pemetrexed or paclitaxel are included as an option for investigator's choice of PDC. In CM816, for the nivo+PDC and PDC only arms respectively, [redacted] patients received a cisplatin-based regimen and [redacted] patients received a carboplatin-based regimen. In the metastatic NSCLC setting, equivalence between carboplatin-based and cisplatin-based chemotherapy was assessed in a meta-analysis of 12 RCTs; no difference was found in overall survival[2]. The feasibility of conducting a similar analysis was assessed in the non-metastatic setting; only two studies were identified that compared the same 2nd agent and as a result, a meta-analysis was not recommended. Despite this, the two identified studies reflect comparable outcomes for overall survival[3,4]. Finally, a 2014 meta-analysis conducted by the NSCLC Collaborative Group in the neoadjuvant setting assessed the overall survival of cisplatin-based vs carboplatin-based regimens (a prespecified subgroup analysis) and found no significant difference in overall survival[5]. Given the findings above, alongside the design of CM816 (investigator's choice of carboplatin-based or cisplatin-based PDC regimens) and the relatively small proportion of patients receiving carboplatin-based PDC, BMS propose to consider all cisplatin-based and carboplatin-based PDC regimens as equivalent within our economic analyses. One additional reason for assuming equivalence in carboplatin-based and cisplatin-based PDC is that the NATCH trial (Felip 2010)[6], where patients received carboplatin-based PDC only, is the only identified randomised controlled trial connecting	evaluation, identifying comparators should be inclusive'. Therefore, the list of comparators in the final scope is kept broad so as not to exclude any potentially relevant comparators that are established practice in the NHS. The scope has been updated to include 'adjuvant chemotherapy' as a comparator to be inclusive of all chemotherapy regimens, including different combinations of platinum-doublet therapy.

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		neoadjuvant PDC to adjuvant PDC in BMS' indirect treatment comparison network. **2. Adjuvant Atezolizumab:** Substantial heterogeneity is present in a comparison between IMpower-010 (adjuvant atezolizumab) and CM816 (nivo+PDC). A main confounder in the comparative treatment effect between CM816 and IMpower-010 is the required use of four cycles of adjuvant PDC in IMpower-010 before atezolizumab is administered. Other potential confounders include: • Patients in CM816 were randomised before surgery (potentially resectable patients), whilst patients in IMpower-010 were randomised after complete resection (completely resected patients). Completely resected patients are a subset of all potentially resectable patients. • A large magnitude of difference in treatment duration (3 cycles vs 18) • Different primary endpoints (disease-free survival vs event-free survival), whereby disease-free survival does not capture progression of disease preventing surgical resection by definition. This heterogeneity leads to several assumptions being required to compare CM816 to IMpower-010. The credibility of such an indirect comparison is therefore substantially reduced compared to a standard indirect treatment comparison. Finally, a key difference between neoadjuvant nivo+PDC and adjuvant atezolizumab is that the anticipated marketing authorisation for neoadjuvant nivo+PDC is for PD-L1 all-comers, whereas the final marketing authorisation for adjuvant atezolizumab covers patients that are PD-L1>50% only. BMS maintain that the current standard of care for patients with resectable NSCLC, and therefore the most appropriate comparator for nivo+PDC, is	The presence of heterogeneity for conducting any relevant comparisons of nivolumab with chemotherapy versus any current therapy or the use of any current therapy in a subgroup of the patient population included in this scope does not justify its relevance as an inappropriate comparator.

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		surgical resection followed by adjuvant PDC (when tolerable) or surgical resection alone.	
	British Thoracic Oncology Group	NICE guidelines appropriately quoted. However, comparator groups should only include patients with stage IB-IIIA NSCLC deemed potentially operable, both technically and medically	Comment noted. No action required.
Outcomes	Bristol Myers Squibb	In addition to those listed in the scope, event-free survival and pathological complete response should be included as the two primary endpoints of the CM816 trial. Time to distant metastases or death should also be included as a secondary endpoint of the CM816 trial.	Thank you for your comment. 'Response rates' captures different response measures (including complete response). The list of outcomes measures in the scope is not intended to be exhaustive. No action required.
	British Thoracic Oncology Group	Yes, but more detailed outcome measures related to surgical morbidity and mortality rates should be defined. Consideration of description and recording of Major Pathological Remission (MPR) rates. Also, immunotherapy related toxicity scoring important.	Thank you for your comment. The list of outcomes measures in the scope is not intended to be exhaustive. No action required.
Economic analysis	Bristol Myers Squibb	No comments.	Comment noted.

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	British Thoracic Oncology Group	Cost effectiveness analysis will need to consider a time period of at least 5 years, as the treatment intent is curative, and benefits may therefore be maintained in the long term	Comment noted. No action required.
Equality	Bristol Myers Squibb	There are no equality issues associated with this appraisal.	Comment noted. No action required.
	British Thoracic Oncology Group	No issues with equality or discrimination	Comment noted. No action required.
Other considerations	Bristol Myers Squibb	No comments.	Comment noted.
	British Thoracic Oncology Group	A number of other IO agents are being trialed in this therapeutic area. Understanding of the current phase II data and ongoing phase III studies with Atezolizumab, pembrolizumab and Durvalumab will be important for NICE to assess and consider	Comment noted. No action required.
Innovation	Bristol Myers Squibb	About half of patients with NSCLC are diagnosed with a non-metastatic disease and rates are expected to rise. Despite potential eligibility for curative surgery, up to 55% of patients who undergo resection develop recurrence and ultimately die of their disease[5]. Neoadjuvant or adjuvant PDC could be utilised in patients with high risk of recurrence, but treatment rates remain low, possibly due to modest survival improvement observed (+5% absolute OS benefit at 5 years versus surgery alone)[7]. CheckMate 816 builds on a strong biological rationale to use immunotherapy in the neoadjuvant setting, before surgery, when the presence of a tumour and draining lymph nodes may enable a stronger anticancer immune response, representing the earliest opportunity as well to target micro-metastases. CheckMate 816 is the first and currently the only positive phase 3 clinical trial with an immunotherapy-	Thank you for your comments. The extent to which the technology is innovative will be considered by the appraisal committee based on evidence presented to it. No action required.

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		based combination in the neoadjuvant setting of NSCLC to demonstrate statistically significant and clinically meaningful event-free survival and pathological complete response improvement, as well as a promising indication of an overall survival benefit in the interim analysis. Feasibility of surgery was preserved when adding nivo to neoadjuvant PDC, and tolerability was maintained. Consistent benefit of nivo+PDC was observed across 1) all survival-related (event-free survival, time to death or distant metastasis, and event-free survival), 2) pathological (pathological complete response and major pathological response), and 3) radiographic (objective response, downstaging) endpoints, showing potential for long-term benefit. Neoadjuvant nivo+PDC has been described by clinical experts as 'paradigm changing' for patients with resectable NSCLC in the UK[8].	
	British Thoracic Oncology Group	Yes, this is a innovative approach with exciting Phase II data with a number of IO agents, including increased pathological CR rates. This is now confirmed in the phase III CHECKMATE 816 trial setting. Potential increased cure rates would mean more long term survivors, which QALYS may not take into account.	Thank you for your comments. The extent to which the technology is innovative will be considered by the appraisal committee based on evidence presented to it. No action required.
Questions for consultation	Bristol Myers Squibb	*Would nivolumab with chemotherapy be a candidate for managed access?* BMS anticipate that nivo+PDC will be suitable for routine commissioning, however nivo+PDC may be considered a candidate for managed access if necessary.	Comment noted. No action required.

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	British Thoracic Oncology Group	Combination IO and chemo is showing much promise in the neoadjuvant setting, and CHECKMATE 816 is the first Phase III trial to show improvements in event free survivals. Results of other phase III studies using different IO agents are eagerly anticipated eg KEYNOTE-671 (Pembro), IMpower30 (Atezo), AEGEAN (Durva)	Comment noted. No action required.
Additional comments on the draft scope	Bristol Myers Squibb	No comments provided	N/A
	British Thoracic Oncology Group	No comments provided	N/A

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

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