National Institute for Health and Care Excellence

Health Technology Evaluation

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

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	Evaluating this topic via the Single Technology Appraisal (STA) route is appropriate and aligns well with the need to provide patients with additional effective options in a timely manner	Thank you for your comment no action needed.
	Pierre Fabre Ltd	No comment	-
	Melanoma Focus	Yes agree this is appropriate.	Thank you for your comment no action needed.
Wording	Bristol-Myers Squibb	Yes	Thank you for your comment no action needed.
	Pierre Fabre Ltd	No comment	-

Section	Stakeholder	Comments [sic]	Action
	Melanoma Focus	Yes	Thank you for your comment no action is needed.
Timing issues	Bristol-Myers Squibb	No comment	-
	Pierre Fabre Ltd	No comment	-
	Melanoma Focus	Important to do in a timely manner in line with potential licencing of the drug combination in the UK.	Thank you for your comment. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. No action is needed.
Additional comments on the draft remit	Bristol-Myers Squibb	N/A	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bristol-Myers Squibb	No comment	-
	Pierre Fabre Ltd	No comment	-
	Melanoma Focus	Some inaccuracies; the following sentences should read: Stage 3 includes melanoma that has spread to local skin and/or nodes. Approximately 40% of melanomas harbour activating BRAF mutations Dabrafenib or vemurafenib single agents are suitable when combination therapy with MEK inhibitors trametinib and binimetinib are contraindicated. When targeted therapies and immunotherapy treatment are contraindicated, dacarbazine chemotherapy or best supportive care is recommended	Thank you for your comments. The background was updated. The percentage of melanomas with BRAF mutations was not changed as no reference was provided. Ascierto et al. 2012 referenced in the scope state that about 50% of melanomas have BRAF mutations.
Population	Bristol-Myers Squibb	The population is aligned to the proposed regulatory label	Thank you for your comment no action is needed.
	Pierre Fabre Ltd	No comment	-

Section	Consultee/ Commentator	Comments [sic]	Action
	Melanoma Focus	yes	Thank you for your comment no action is needed.
Subgroups	Bristol-Myers Squibb	It is anticipated that nivolumab-relatlimab will be used in patients with previously untreated unresectable or metastatic melanoma who are suitable for immunotherapy regardless of PD-L1 and BRAF status. As discussed below, the BRAF status of the patient is not a key factor in first- line treatment choice for patients who are suitable for immunotherapy, and therefore is not a relevant subgroup for this appraisal. PD-L1 testing is not routinely carried out for melanoma patients in the UK and there are concerns from the clinical community regarding the validity of this biomarker in treatment choices (due to the transient/dynamic nature of the biomarker and variation in assays). Therefore, determining the PD-L1 status of a patient is not a key factor in the UK melanoma treatment decision pathway, as such, subgrouping of patients on their PDL-1 status is not relevant for this appraisal. This is aligned to the committee decision in the nivolumab + ipilimumab appraisal where it was noted "*PD-L1 expression is not routinely assessed in clinical practice. Furthermore, there is no universally agreed threshold for PD-L1 expression. The committee concluded that PD-L1 expression may be one of the factors that influence clinical decision making, but it would not be appropriate for NICE to base recommendations on PD-L1 expression at present.*"	Thank you for your comments. We have heard from other stakeholders that both subgroups are appropriate. There will be an opportunity to justify why these sub-groups should or not be considered in your submission.
	Pierre Fabre Ltd	No comment	-

Section	Consultee/ Commentator	Comments [sic]	Action
	Melanoma Focus	yes	Thank you for your comment no action is needed.
Comparators	Bristol-Myers Squibb	Based on the recently updated NICE melanoma guidelines,[1] initial treatment decisions are based on suitability for immunotherapy, rather than *BRAF* mutation status. *BRAF* inhibitors are only recommended for patients if immunotherapy is contraindicated or unsuitable – therefore as nivolumab-relatlimab is an immunotherapy, BRAF/MEK targeted combination therapies trametinib with dabrafenib and encorafenib with binimetinib, are not considered to be comparators of interest. For patients who are suitable for immunotherapy, NICE guidelines recommend nivolumab + ipilimumab combination therapy as first choice if suitable/acceptable for the patient. If combination treatment is unsuitable, immunotherapy monotherapy (nivolumab or pembrolizumab) should be used. The use of ipilimumab monotherapy is not recommended at first line within the NICE guidelines, and based on clinical opinion, ipilimumab monotherapy would only be used in subsequent treatment lines if it had not been received as part of combination treatment at first-line. Hence, appropriate comparators for this appraisal are: • Nivolumab • Pembrolizumab • Nivolumab + ipilimumab	Thank you for your comments. Targeted therapies have been removed from the list of comparators.
	Pierre Fabre Ltd	All the relevant comparators have been included in the scope.	Thank you for your comments. Targeted

Section	Consultee/ Commentator	Comments [sic]	Action
		Ipilimumab monotherapy is not an appropriate comparator and previous appraisals (TA384 and TA400) have demonstrated that nivolumab and nivolumab with ipilimumab, both listed comparators for this appraisal, to be both more effective than ipilimumab monotherapy at least in the short term. It is appropriate to exclude the BRAF inhibitor monotherapies (dabrafenib and vemurafenib). Dabrafenib and vemurafenib, while recommended as monotherapy within the current NICE melanoma guidelines, are only recommended if immunotherapy and targeted therapy combinations are both unsuitable or unacceptable to the patient. Within clinical practice the monotherapies are therefore rarely used and are not considered standard of care.	therapies have been removed from the list of comparators.
	Melanoma Focus	Yes	Thank you for your comment. Please note that based on other stakeholders' comments, targeted therapies have been removed from the list of comparators.
Outcomes	Bristol-Myers Squibb	Yes, the outcomes listed are appropriate.	Thank you for your comment no action is needed.
	Pierre Fabre Ltd	No comment	-

Section	Consultee/ Commentator	Comments [sic]	Action
	Melanoma Focus	Yes	Thank you for your comment no action is needed.
Equality	Bristol-Myers Squibb	No equality considerations relating to the use of nivolumab-relatlimab have been identified or are anticipated except that melanoma is relatively more prevalent in lower socioeconomic groups. Improving outcomes for these groups is in line with NICE's *"Principle 9. Aim to reduce health inequalities"*	Thank you for your comment no action is needed.
	Pierre Fabre Ltd	No comment	-
	Melanoma Focus	No additional comments	-
Other considerations	Bristol-Myers Squibb	NA	-
	Pierre Fabre Ltd	No comment	-
	Melanoma Focus	No additional comments	-
Questions for consultation	Bristol-Myers Squibb	**Where do you consider nivolumab-relatlimab will fit into the existing care pathway for untreated unresectable or metastatic melanoma?** Based on the recently updated NICE melanoma guidelines,[1] initial treatment decisions are based on suitability for immunotherapy. We anticipate that nivolumab-relatlimab, which is the first dual fixed dose immunotherapy synergistically targeting PD-L1 and LAG-3 will provide an additional treatment option for patients who are suitable for immunotherapy. Despite the	Thank you for your comments. No action is needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		availability of dual immunotherapy, current dual therapies are associated with additive toxicity and are not appropriate for all patients. There is a need for further treatments that can improve on single-agent PD-1 inhibitors, with a safety profile that is generally manageable with standard protocols, to allow even more patients with metastatic melanoma to derive long-term benefit from dual immunotherapy therapy. **Would nivolumab-relatlimab be a candidate for managed access?** No **Would it be appropriate to use the cost-comparison methodology for this topic?** It is anticipated that nivolumab-relatlimab will provide similar clinical efficacy to nivolumab + ipilimumab, so a cost comparison methodology could be used for this comparison. However, the other comparators (nivolumab and pembrolizumab) will require a fully incremental cost-effectiveness analysis, therefore appraising nivolumab-relatlimab using standard STA methodology is appropriate. **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** [redacted] **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?**	

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		The primary outcome from RELATIVITY-047 is progression-free survival as assessed by a Blinded Independent Central Review (BICR), using RECIST v1.1 and is also aligned with the primary outcome for the CheckMate 067 pivotal trial for nivolumab + ipilimumab which was used for decision making by NICE within its appraisal.[2] **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** We will be carrying out a clinical SLR to ensure that all relevant recent evidence for comparators is considered. We are not aware of any upcoming publications for comparator trials within the timeframe of the appraisal which would not be identified through the SLR process.	
	Pierre Fabre Ltd	No comment	-
	Melanoma Focus	No additional comments	-
Additional comments on the draft scope	Bristol-Myers Squibb	NA	-

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

None.