National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Atezolizumab monotherapy for untreated PD-L1 positive metastatic non-small-cell lung cancer

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
Appropriateness	Roche	No comment received	N/A
Wording	Roche	The wording does not reflect the population under consideration in terms of PD-L1 expression. Our alternative suggested wording is: “To appraise the clinical and cost effectiveness of atezolizumab monotherapy within its marketing authorisation for untreated PD-L1 positive metastatic non-small-cell lung cancer.”	Comment noted. The draft remit has been updated to reflect these comments.
Timing Issues	Roche	We consider that this appraisal is eligible for fast track appraisal for reasons described in the “Questions for consultation” section. This will help enable access for patients as soon as possible after marketing authorisation.	Comment noted. The company can propose a fast track (FTA) application. Any such application will be reviewed by NICE to assess the most appropriate process. No changes to the draft scope required.

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Additional comments on the draft remit	Roche	No comment received	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche	We noted the following inaccuracies and omissions in the background information section: • Reference is made to NICE clinical guideline 121; this guideline has been superseded by NICE guideline 122. • The statement "For squamous NSCLC that has not progressed immediately following initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance treatment with pemetrexed is recommended as an option" is incorrect. Pemetrexed is neither licensed nor NICE recommended in this setting. • A therapeutic option for squamous NSCLC is missing. NICE TA600 recommends pembrolizumab, with carboplatin and paclitaxel for use within the Cancer Drugs Fund as an option for untreated metastatic squamous NSCLC.	Comments noted. The draft scope has been updated to reflect the comments received.
The technology/ intervention	Roche	No comments.	Comment noted. No action required.
Population	Roche	In order to define relevant comparators, some further definition of the population is required. The proposed indication is [redacted] We would therefore suggest amending the population to	Comments noted. The current wording is appropriate as it covers the population referred to. NICE will appraise

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		"Adults with non-squamous or squamous untreated metastatic NSCLC with high PD-L1 expression and without EGFR- or ALK-positive mutations".	atezolizumab within its marketing authorisation. No changes to the draft scope required.
Comparators	Roche	**Non-squamous NSCLC:** We consider that the only clinically relevant comparator for non-squamous NSCLC is pembrolizumab monotherapy for the following reasons: • Atezolizumab plus bevacizumab, carboplatin and paclitaxel is not an appropriate comparator as it is only recommended in patients with PD-L1 expression between 0% and 49%. • Of the chemotherapy combinations listed, we consider that the only combination in regular use is pemetrexed plus a platinum drug with or without pemetrexed maintenance. Pemetrexed plus platinum is the standard of care (SoC) chemotherapy regimen for patients with first-line non-squamous NSCLC, based on both clinical expert opinion as well as market share data (Roche data on file). Whilst the other platinum drug partners listed in the draft scope (docetaxel, gemcitabine, paclitaxel or vinorelbine) are treatment options for first-line NSCLC, they are not commonly used for non-squamous histology. As such, these chemotherapy options should not be considered relevant comparators for this appraisal. In addition, while a minority of PD-L1-high patients are still treated with chemotherapy alone, this is usually for reasons of ineligibility for treatment with immunotherapy. Consequently, we consider that chemotherapy alone is not a relevant comparator for this appraisal. • A survey of 30 UK-based lung oncologists conducted by Roche showed that approximately 70% of PD-L1-high non-squamous patients are treated with pembrolizumab monotherapy, with only 4.5% receiving chemotherapy alone. The remaining patients received	The comparator section in the draft scope has been updated to reflect both histology status and PD-L1 tumour expression level. The company can comment on the relevance of any comparator in its submission.

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		pembrolizumab plus cisplatin or carboplatin plus pemetrexed, which is not in the scope of this appraisal, since it is funded through the CDF. **Squamous NSCLC:** We consider that the only clinically relevant comparator for squamous NSCLC is pembrolizumab monotherapy for the following reasons: • A minority of PD-L1-high patients are still treated with chemotherapy alone. However, this is usually for reasons of ineligibility for treatment with immunotherapy. Consequently, we consider that chemotherapy alone is not a relevant comparator for this appraisal. • A survey of 30 UK-based lung oncologists conducted by Roche showed that approximately 86% of PD-L1-high squamous patients are treated with pembrolizumab monotherapy, with only 5% receiving chemotherapy alone. The remaining patients received plus carboplatin plus plus paclitaxel, which is not in the scope of this appraisal, since it is funded through the CDF. Overall, based on the decision problem population, prior knowledge of the therapy area and clinical expert advice, we regard pembrolizumab monotherapy to be the only clinically relevant comparator for this appraisal.	
Outcomes	Roche	We agree with the listed outcome measures, though we would recommend including duration of response in addition as this is a clinically relevant endpoint for cancer immunotherapies, which are characterised by durable responses.	Comments noted. The list of outcomes in the draft scope is not exhaustive. The company can present additional outcomes as supplementary information supported with appropriate

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			rationale. No changes to the scope required.
Economic analysis	Roche	The economic analysis will follow the NICE reference case.	Comment noted. No action required.
Equality and Diversity	Roche	No equality issues were identified.	Comment noted. No action required.
Other considerations	Roche	Subgroup analysis by level of PD-L1 expression is not appropriate for this appraisal since the population is already limited to one PD-L1 expression level (see response to population section). The IMpower110 study included patients with both squamous and non-squamous histology. However, the trial was not statistically powered to assess efficacy in either subgroup. Consequently, subgroup analysis by histology is not appropriate.	Comments noted. Subgroup analysis should be explored if the evidence allows. The company can comment on the data available for such comparisons. No changes to the draft scope required.
	Royal College of Pathologists	The role of tumour mutation burden in patient selection. This is not currently available in most NHS laboratories. Emerging evidence suggests it may be an effective means of patient selection for atezolizumab. The benefits this technology may offer in this setting needs to be taken into account as it will have important implications for testing laboratories. If this is to be done on peripheral blood this would ease the pressure of testing on the primary biopsy which is already being used for EFGR, ALK ROS1 and of course the diagnosis. In the event that very precise PD-L1 expression levels prove critical to the selection of the best check point inhibitor, consideration should be given to	Comments noted. All relevant testing methods will be considered by the committee.

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		how reproducible such assessments may be, when performed on small biopsies, and cytology samples	
Innovation	Roche	Atezolizumab is a humanised monoclonal antibody immunoglobulin IgG1 that binds directly and selectively to PD-L1 immune checkpoint protein, thus preventing it from binding to receptors PD-1 and B7.1. This prevents down-regulation of T cell activity, allowing for the priming of new T cells to facilitate anticancer immune responses. In parallel, the PD-L2/PD-1 interaction is left intact, potentially preserving peripheral immune homeostasis. It is the first PD-L1 inhibitor to demonstrate efficacy in a treatment-naive, high PD-L1 NSCLC population, with an overall survival hazard ratio of 0.59 versus standard chemotherapy. Atezolizumab monotherapy also offers dosing flexibility, with the option of administration every two, three or four weeks.	Comments noted. The company will have the opportunity to expand on the innovative potential of this technology in its submission and this will be considered by the appraisal committee
	Royal College of Pathologists	The technology is innovative. Check point inhibitors are proving to be effective in some patients with advanced non small cell carcinoma. The addition of new agents is likely to be beneficial to some patient groups. See PubMed ref PMID	Comments noted. The potential innovation can be expanded up on in the evidence submissions and will be considered by the appraisal committee.
Questions for consultation	Roche	Most questions have been answered in prior sections. Responses to new questions are below: **“Where do you consider atezolizumab will fit into the existing NICE pathway for lung cancer?”**	Comments noted. Please see relevant responses in the sections above.

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		We consider that atezolizumab in the proposed indication will fit into the NICE lung cancer pathway alongside pembrolizumab monotherapy in untreated PD-L1-positive metastatic non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 (TA531). **"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?"** We do not consider that there will be any barriers to adoption of this technology into practice. **"Would it be appropriate to use the cost comparison methodology for this topic?"** We consider pembrolizumab monotherapy to be the primary comparator for this appraisal, and that it may be appropriate to use cost comparison methodology for this topic, for the reasons given in response to the following question. **"Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?"** Yes, pembrolizumab monotherapy has demonstrated similar overall survival hazard ratios in PD-L1-high patients in both the KEYNOTE-024 study (0.60, 95% CI: 0.41, 0.89) and in the equivalent population of the KEYNOTE-042 study (0.69, 95% CI: 0.56, 0.85), as compared with IMpower110 (0.59, 95% CI: 0.40, 0.89). In addition, both products are intravenously-administered with a standard three-weekly dosing regimen. Finally, both products are cancer immunotherapies targeted at the PD-1/PD-L1 immune checkpoint; consequently, the toxicity profile of both products could be regarded as similar.	

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		"Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?" Yes, overall survival is a gold standard endpoint in NSCLC. **"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?"** Not that we are aware of.	
Additional comments on the draft scope	Roche	It should be noted that the PD-L1 assay used in the IMpower110 trial, SP142, measured PD-L1 expression on both tumour cells and immune cells, while the PD-L1 assay used in the pembrolizumab trial programme measured PD-L1 expression on tumour cells only. However, we have conducted an assay comparison study on the IMpower110 trial population, published at the IO-ESMO conference in December 2019, which demonstrated comparable outcomes regardless of the assay used. A similar assay comparison conducted on the atezolizumab OAK trial data in 2L NSCLC also showed similarly comparable outcomes between assays. Consequently, we consider that the use of differing assays does not significantly affect the patient population in question.	Comments noted. This issue will be considered within the appraisal. No changes to the draft scope required.

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

Pierre Fabre

Merck Sharp & Dohme